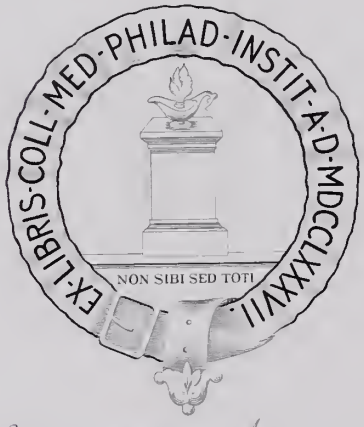
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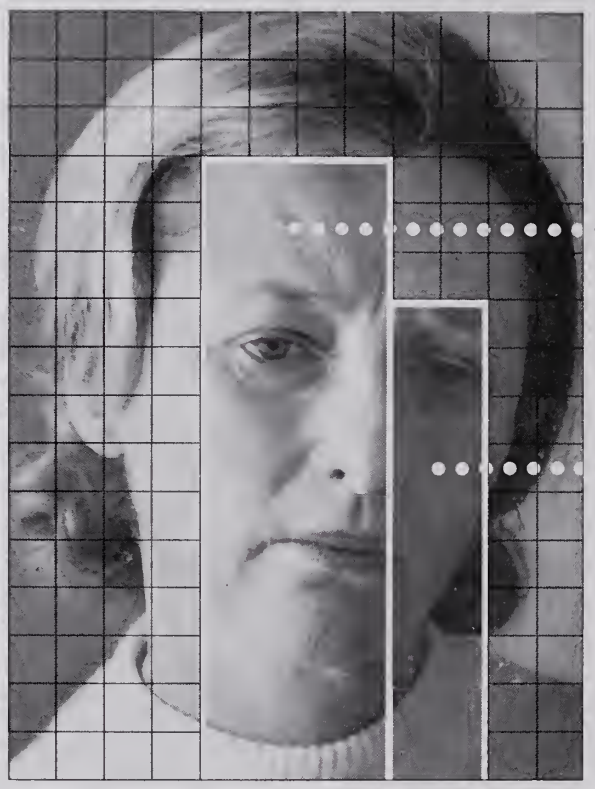

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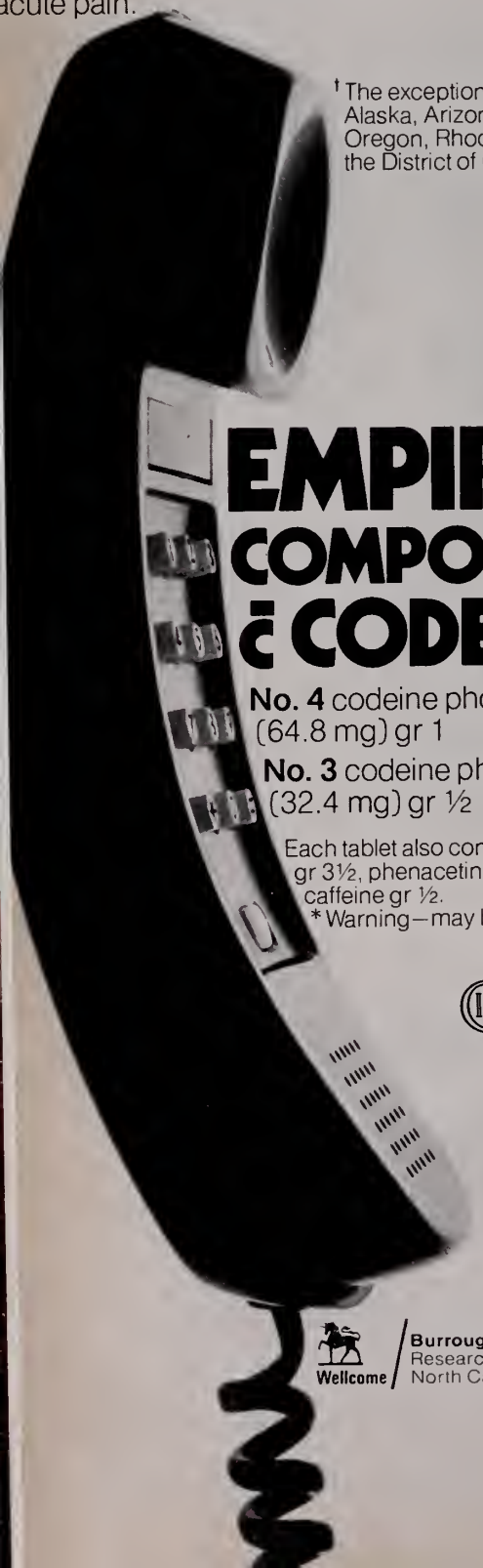
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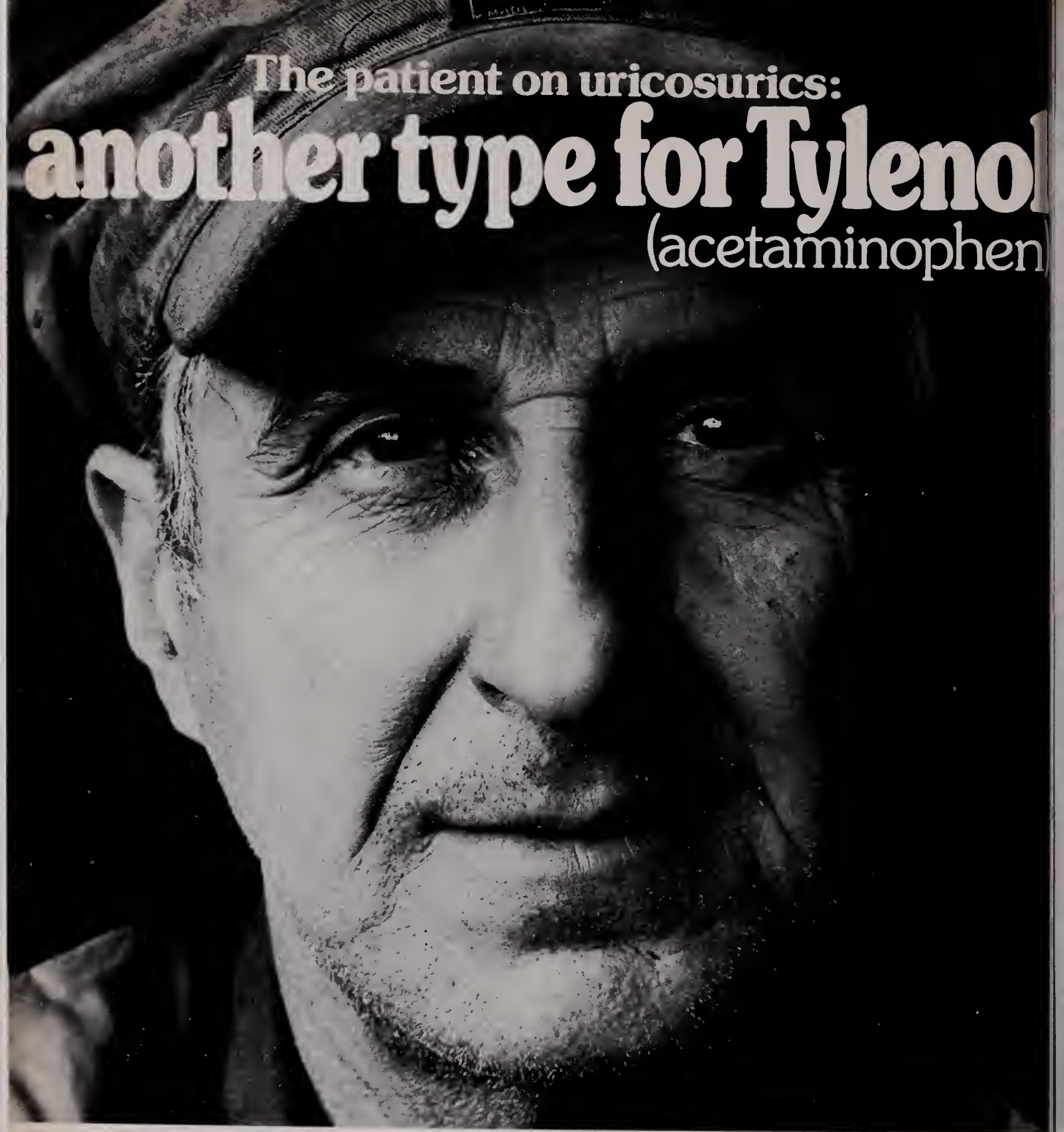
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President's Letter

Heritage of Criticism

THIS IS THE traditional time of year when we take reluctant looks at ourselves and resolve to be and do better. Self-assessment is rarely pleasant, and New Year resolutions are usually long-forgotten by spring.

Recently, physicians have been subject to year-round assessments. Legislators, journalists, and patients are increasingly critical of our prices, our organization, and our services. But criticism of the medical profession is hardly a new phenomenon.

The doctor has been a favorite and easy target for centuries. In medieval times, the doctor, in collusion with the apothecary, was commonly caricatured as profiting from the misery of others. Poor Richard was only giving expression to a widely-held belief when he wrote in his *Almanac* that "God heals, and the doctor takes the fees." Even the criticism by legislators is traditional. Thomas Jefferson was hardly an admirer of the medical profession; he remarked on one occasion that he never saw three physicians talking together, without glancing up to see if there were not a turkey-buzzard hovering overhead.

In a sense this criticism, and perhaps even fear, of the doctor and his ministrations is understandable. Unless we are ill or have recently recovered by virtue of those ministrations, the doctor may not be our favorite person. He sees us at our most miserable, and he is a reminder of our frailty.

But there seems to be a new element in the criticism we now face. Jefferson may have mistrusted physicians, but he would not have set them apart as a group. He would have been unlikely to consider legislation to regulate not only their activities, but also their relationship with their patients.

Criticism by the news media seems to have become constant. It is the journalist's business to report the exception rather than the rule. We can respond to their reports of poor health care, inadequate delivery systems, and exorbitant prices with the results of a recent Minnesota poll in which eighty-five percent of those questioned were satisfied with their medical care. We can point to a similar poll last year in which only five percent felt that health care was one of the major legislative problems.

There are indeed shortcomings to medicine as it is practiced. Some changes are inevitable and necessary. Legislative and journalistic criticism, if it results in thoughtful and constructive change, is valuable.

But the criticism from our patients is most important, for it stems from our actions as individual members of the profession, not from some group such as "organized medicine" or "the AMA." If even five percent of our patients are questioning our commitment, we must question it too. Do we place our well being before that of society and our patients? Are we open and truthful with our patients? Do we do only that for which we are qualified? Are our services prompt and delivered in surroundings that we, as patients, would appreciate? Are our charges fair? Are they more than we would like or be able to pay? Do we relate well to our patients? Are we too busy? Do we really care?

These are questions we must ask and answer. They seem to be the basis of most patient complaints. Our patients are our real critics; if we heed their criticism, our other critics will be silenced.

This is the new year. It is too late for easy resolutions, but reassessment can come at any time.

Bernard Hall M.D.

President
Minnesota State Medical Association

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Editor's Notebook

On Becoming Editor

With this issue of MINNESOTA MEDICINE, Reuben Berman becomes Editor-Emeritus, and the editorship passes into my hands. The first question that may come to mind is: "What changes will be made in MINNESOTA MEDICINE?"

With Reuben's track record, I think the answer has to be: "Not many." I've heard few criticisms and many compliments on the journal during his three years at the helm. And I'm not one to stir calm waters.

During his editorship, Reuben was able to recognize, encourage, and mobilize material for special issues from within the State of Minnesota. The recent dermatologic issue (the one with the extraordinary photographs of skin lesions) is an example. So is this issue, which brings together papers on Nephrology from the Mayo Clinic, the University of Minnesota, Hennepin County Hospital, and Methodist Hospital in Minneapolis. Reuben has used the journal to unify and integrate knowledge from different parts of the state, and in the process has left me a backlog of good material.

There will be one change: This Editor's page, which I shall call "Editor's Notebook." It will appear next to the table of contents. Here I may write an essay, introduce an issue, sally into the scientific arena, or even compose a poem.

Like most Editors, I think of myself as a writer. This page helps me air that fancy. Besides, an introductory piece it gives me a chance to set a tone and pace for the journal. Don't take me too seriously. I'm only human, and like most humans, I have my prose and cons.

I'd like to close with a comment on how I feel about writing style. You can be formal, but please don't be stuffy or vague. The best writing, scientific or otherwise, is direct, clear, and concise. And remember: publication in this journal costs almost 10 cents a word. When submitting manuscripts, keep that dime in mind. Even when you finish your final draft, try to shorten each sentence (or omit it). You will achieve economy, and clarity.

The Board of Editors joins me in wishing you a happy 1975.

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Urinalysis and Other Tests of Renal Function

DAVID M. WILSON, M.D.*

The urinalysis and creatinine clearance pose common pitfalls in patient preparation, performance of the tests and interpretation.

EXAMINATION OF THE urine can be utilized to assess the metabolic status of the patient—for example, to test for absence of antidiuretic hormone (ADH) or for excess of a specific hormone as in aldosteronism or pheochromocytoma. It also can reflect abnormal function of other organs—for example, by the presence of bilirubinuria, ketonuria, or increased amylase. Examination of the urine may be most useful as a way of assessing kidney function and will be reviewed here in this light.

In the normal adult, blood passes through the kidney at a rate of about 1.2 liters/min. Of the 600 ml of plasma, about one-fifth is filtered through the glomeruli. The ultrafiltrate contains virtually all the nonprotein components of plasma. The pH and osmolality of the filtrate are the same as those of plasma. To maintain homeostasis this filtrate is modified by several distinct mechanisms as it passes down the tubule into the urinary bladder. Glucose, amino acids, proteins, sodium, potassium, phosphates, uric acid, and bicarbonate are variably reabsorbed from the proximal tubule, usually with a threshold for this transport process. Secretion of uric acid, potassium, hydrogen ion, and other substances such as glucuronides and penicillins is accomplished along the nephron. These processes are variably linked to negative feedback mechanisms that respond to aldosterone, P_{CO_2}, cellular level of potassium, and plasma levels of some substances.

Ninety percent of the fluid is reabsorbed by the time the ultrafiltrate reaches the distal tubule, whether the subject is in a state of hydration or dehydration. In the distal tubule and collecting duct more water is reabsorbed under the regulatory influence of ADH to maintain water homeostasis. At this distal site acidification of the urine and potassium excretion occur, along with the final regulation of many substances that were not reabsorbed in the proximal tubule.

In general the composition of the urine reflects the status of hydration, the dietary intake, and the basal metabolic production of many of the substances mentioned. A decision as to whether kidney function is impaired requires knowledge of or regulation of intake or metabolism to permit interpretation of excretion data as reflecting abnormalities of renal function. Several examples of this principle are the following: (1) knowledge of potassium intake or potassium balance in assessing whether a given level of potassium excretion indicates renal impairment in potassium handling; (2) knowledge of fluid intake in assessing impairment of renal concentrating ability; and (3) knowledge of the previous exercise or body temperature of the patient in assessing protein excretion in the urine. For tests that are performed as part of a routine urinalysis, conditions are difficult to control but can be standardized in a way that allows interpretation of the results under most circumstances.

Tests of Concentrating Ability

Concentration tests indicate the ability of the kidneys to develop a high concentration in the interstitial fluids of the medulla, and this concentration depends on the active transport of solute from the ascending loop of Henle and the distal convoluted tubule. The osmolality and specific gravity of the urine are the two measurements used.

The specific gravity is the ratio of the weight of a volume of urine to the weight of the same volume of distilled water at a constant specific temperature. The density of the urine depends not only on the number of solute molecules and

*Director, Renal and Electrolyte Laboratory, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

ions in it but also on their density. Large molecules such as glucose and protein have a greater effect on the specific gravity than on the osmolality. The very dense molecules such as intravenous pyelogram dyes have a profound effect on the specific gravity of urine, with values as high as 1.050 being observed. We therefore have to be aware of these exogenous materials and to correct for glucose or protein in the urine. The specific gravity of the urine is increased by 0.001 by glucose at 0.27 g/dl or by protein at 0.4 g/dl.

The measurement of osmolality is more physiologic in the sense that it measures the function of the kidney more appropriately than does the specific gravity. Techniques for measuring osmolality have been cumbersome and take more time and more equipment, so that osmolality measurements have not been part of routine urinalyses in most laboratories. However automation of osmometers makes osmometry feasible. A new method of measuring the osmolality, by using dew point depression, which requires only 30 seconds per sample has recently been introduced.

The concentration of the urine may be used as a test of renal function. However, several nonrenal diseases, such as diabetes insipidus, can decrease the urine osmolality. Other factors that may interfere with the ability to concentrate urine are abnormalities in electrolytes (such as potassium and calcium), protein malnutrition, and polydipsia. Some drugs (such as corticosteroids) and, of course, diuretics (such as thiazides and mannitol) may alter the urine osmolality.

A marked decrease in glomerular filtration will limit the capacity of the tubule to present sodium to the concentration sites of the medulla and therefore will also impair the ability to concentrate the urine. The normal adult on a normal diet with normal fluid intake will produce a urine of about 500 to 850 mosmol/kg water. The normal kidney, is able to produce urine of osmolalities ranging from 800 to 1,400 mosmol/kg under dehydration and of a minimal osmolality of 40 to 80 mosmol/kg during water diuresis. It has been established that in most persons the maximal concentrating ability occurs after 30 hours of dehydration—after 14 hours of dehydration, only about 65% of patients will have approached their maximal osmolality.

Usually an overnight urine specimen will have an osmolality greater than 800 mosmol/kg, and the specific gravity will be greater than 1.022. A more exacting test of concentrating ability would be to dehydrate the patient for 30 hours; under these circumstances an osmolality greater than 850 mosmol/kg should be achieved. A modification of this procedure performed in many laboratories involves 12 to 14 hours of dehydration and the administration of vasopressin (Pitressin) (100 milliunits subcutaneously or 5 milliunits/min infused over a period of an hour) followed by four one-hour urine collections. The highest value in these four hours is taken as the maximal osmolality.[1]

The urine concentrating ability should be interpreted in the light of other tests of renal function. For example the relationship between glomerular filtration rate and concentrating ability may be useful in understanding the primary disease process. The glomerular filtration rate is restricted more than the concentrating ability of the kidney in diseases in which the glomerulus is more involved than the tubules, such as the nephrotic syndrome or acute glomerulonephritis. Similar decreases of the glomerular filtration rate and the concentrating ability are often seen in chronic glomerulonephritis or glomerulosclerosis. A decrease of the concentrating ability greater than that of the glomerular filtration rate often indicates that the disease process involves primarily the tubules—for example, polycystic disease, pyelonephritis, or analgesic nephropathy.

TABLE 1
Reported Normal Urinary Protein Excretion Rates

Author	Mean total protein (mg/24 h	Comment
Rigas & Heller[3] (1951)	39.0 ± 5.7	Albumin 14.8 ± 2.2; globulin 25.8 ± 3.9
Webb et al.[4] (1958)	133	23% albumin
Melo etal.[5] (1959)	126.3 (range, 90.5—167.8)	
Jørgensen[6] (1967)	118.7 ± 18.5*	Males, 122.3 ± 16.8; females, 115.3 ± 19.8

*Per 1.73 m^2 body surface area.

Urinary Protein

Proteinuria is the most common indicator of renal disease. It is an early indication of latent tubular disease, glomerulonephritis, toxemia of pregnancy, and diabetic nephropathy. The quantitative increase or the type of proteinuria may suggest the presence of renal disease as opposed to urinary tract disease, particularly when considered with the clinical findings. Normal urine contains small amounts of protein. These amounts vary with the analytical method used as well as with the duration of the urine collection and the control of posture, exercise, and fluid intake. As reviewed by Rennie,[2] a protein excretion rate less than 150 mg/24 h is probably normal (Table 1).

The screening test for proteinuria now most often used is the dipstick method which involves alteration of an indicator dye by protein in the solution. False-positive reactions for protein are rare with this method and are found only in highly buffered alkaline urines. Protein excretion rate shows no relationship to age. With the dipstick method, the incidence of proteinuria (greater than 1 +) is 5.2% in students, which is similar to the 1 to 5% found by Bernard et al.[7] in a review of published reports of proteinuria in young servicemen. False-negative reactions occur primarily in urine specimens that are dilute, which is the reason that many laboratories still rely on sulfosalicylic acid or heat and acetic acid methods; these methods have about double the sensitivity of the dipstick method. The dipstick method is sensitive to about 30 mg of albumin/dl.

The method using heat and acetic acid is much better as a screening test because many patients have dilute urine. It and the sulfosalicylic acid method can give false-positive reactions in the presence of various substances (Table 2). These false-positive results are not difficult to recognize because most of them cause a turbidity that is different from that produced by the proteins. A positive result on a screening test for proteinuria may have grave significance and therefore it is important to be able to confirm it by a second screening method; the heat and acetic method is usually one of those used after the dipstick test.

Qualitative, semiquantitative, and differential protein studies have their places in evaluating renal function because severe, mild, and minimal proteinuria all have different significance with respect to evaluation of renal disease. The normal glomerular filtration of protein is approximately 8 mg/dl, so that five to 30 g of protein appear daily in the normal glomerular filtrate. Once in the glomerular filtrate, the plasma proteins are for the most part reabsorbed because the normal daily excretion is only about 1% of the amount in the filtrate. With the probable exception of low-molecular-weight proteins, tubular protein reabsorption is unselective.

In the nephrotic syndrome, the primary functional disturbance is increased permeability of the glomerular capillaries. Tubular protein catabolism is also increased owing to the increased intraluminal protein concentration, but the tubular reabsorptive capacity for proteins is apparently overcome and all filtered protein appears in the urine. In other types of renal disease it is not as clear whether the proteinuria is due to tubular damage or to glomerular permeability problems. Various proteins including post-γ-globulin, lysozyme, and ribonuclease are characteristically found in increased amounts in the urine of patients with renal tubular disease. Lysozyme is perhaps the easiest to measure.

Low-molecular-weight proteins are common and have been found to be useful in the diagnosis of Fanconi syndromes and in renal transplant rejection but not in the diagnosis of chronic pyelonephritis. A special instance of this low-molecular-weight protein is the Bence Jones protein. Bence Jones protein is characteristically precipitated in weakly acidic solution at 45° to 60°C and usually redissolves on boiling. Immunoelectrophoretic methods for measuring Bence Jones protein are far superior and are used widely at the present time. These paraproteins do not cause a positive dipstick test although they are detected by the heat and acetic acid method. Proteinuria occurs in 70 to 80% of patients with myeloma; however, only

TABLE 2
False-Positive (+) and False-Negative (−) Reactions With Various Tests for Proteinuria

	Dipstick	Sulfosalicylic acid	Heat and acetic acid
Turbidity	0	Confuse	Confuse
X-ray contrast medium	0	+	+
Tolbutamide	0	+	+
Penicillin	0	+	+
Sulfisoxazole (Gantrisin)	0	+	0
p-Aminosalicylic acid	0	+	0
Albumin, i.v.	+	+	+
Bence Jones protein	−	0	0
Alkaline urine (buffered)	+	−	−
Dilute urine	−	0	0

in about half of these is the proteinuria due to the Bence Jones protein itself. Bence Jones proteinuria is not specific for multiple myeloma and has been seen in cases of lymphoma, leukemia, and other malignancies. The presence of the paraprotein peak in the serum seems to be inversely correlated with its presence in the urine, and the absence of the paraprotein peak in the plasma does not rule out myeloma. This diagnosis may often be confirmed by looking for the paraprotein in the urine.

The degree of proteinuria and the significance of the proteinuria vary with the type of renal disease and the severity of the disease process. Measurement of the amount of protein excreted in the urine is often helpful in diagnosis and in following the course of the disease. Severe proteinuria (greater than 3 g/day) is characteristically seen in patients with a nephrotic syndrome, and oval fat bodies are often present along with edema. It also may be found in patients with glomerular nephritis, lupus nephritis, amyloid, Bence Jones proteinuria, or severe venous congestion of the kidney. Moderate proteinuria (0.5 to 3 g/day) is found in a large number of renal diseases such as chronic glomerulonephritis, nephrosclerosis, tubular interstitial diseases, pyelonephritis, myeloma, diabetic nephropathy, preeclampsia, and various toxic nephropathies including radiation nephritis.

Often in these diseases associated with only moderate proteinuria the urine sediment contains few casts or erythrocytes and little pus.

Carefully taken family, medical, and medication histories are indicated in this setting because one of the common diseases in this group is probably analgesic nephropathy. Other diseases in this category are glomerulonephropathies, asymptomatic obstructive urologic disease, vesicoureteral reflux, sickle cell renal disease, congenital tubular disorders, and heavy metal intoxication.

By far the most common problem is the interpretation of proteinuria in patients with minimal protein excretion in whom the above-mentioned nephropathies are not apparent. If the patient has an abnormal urinary sediment, it often is necessary to proceed to further tests and even renal biopsy in order to establish the diagnosis. Without an abnormal urinary sediment the proper course is not clear. There have been several studies of minimal protein excretion in the past 15 years. It has been common practice to classify this idiopathic proteinuria into persistent proteinuria,intermittent protcinuria, fixed orthostatic proteinuria, and transient orthostatic proteinuria.

On the basis of percutaneous renal biopsies, various morphologic alterations have been described in all but the transient orthostatic group. Persistent and intermittent idiopathic proteinuria have been associated with minor but definite renal changes in 60 to 80% of cases. The lesions are membranous and proliferative type changes, small-vessel abnormalities, and interstitial changes. The significance of these alterations, especially if minor in degree, is not yet known because the incidence of these minor changes in the general population remains undefined. Also, these changes may represent a resolving process from a previous unrecognized renal injury. A recent study of patients with persistent idiopathic proteinuria showed definite renal lesions in most patients, but these did not progress for up to 15 to 18 years after they were found. However, if there were other microscopic findings such as hematuria, the patients often had progressive renal impairment.

In the category of fixed orthostatic proteinuria, the incidence of definite morphologic abnormalities is only about 8%. About 70% of these patients have some sort of proteinuria five years later, and many have urinary sediment abnormalities after this period. However, despite these findings, renal function continues in the normal range. In another study of this same group of patients, evidence of parenchymal renal disease was found in 25% of the cases. Thus, the patients with fixed orthostatic proteinuria may have a 25% chance of having mild abnormalities although renal function has been stable up to 10 years.

There is no satisfactory assessment that will identify the patient at high risk. Mild isolated proteinuria, regardless of the clinical type, generally is associated with a favorable prognosis.

In the last few years it has been shown that, in general, proteins with larger molecular weights are cleared at a lower rate than proteins with lower molecular weights, and it has been suggested that the type of renal disease may be predicted from the relative clearances of proteins of different sizes. Thus, patients with "minimal change" glomerular nephritis with the nephrotic syndrome appear to spill small proteins but not large proteins in the urine and therefore have so-called selective permeability to protein. In other diseases such as membranous glomerulonephritis and diabetic glomerular sclerosis, large as well as small proteins

are excreted. Clinically, the only practical reason for studying selectivity is to determine whether the patient's nephrotic syndrome is due to minimal change disease or the so-called nil lesion. It is not possible at the present time to distinguish other primary renal diseases such as membranous and proliferative glomerulonephritis by such studies.

This method has been simplified and it has been shown that, if two plasma proteins whose molecular weights differ widely are measured in plasma and urine, the relative clearance that can be measured compared well with the methods using five to seven proteins. The absolute concentrations of protein in plasma and in a random urine sample are conveniently measured by radioimmunodiffusion on commercially available plates of agar impregnated with specific antiserums. The greatest accuracy is obtained with albumin and α_2-macroglobulin. There usually is so little α_2-globulin in normal urine that it is difficult to measure unless the urine first is concentrated. Therefore, most laboratories measure protein selectivity with transferrin and IgG or possibly two other proteins. Protein selectivity may be expressed as the selectivity index or ratio of the larger protein clearance to the smaller protein clearance. In one series, only four of 30 patients with minimal change disease had selectivity ratios greater than 0.2 whereas only three of 23 patients with proliferative glomerulonephritis had selectivity ratios less than 0.2.

Hematuria

After proteinuria, the next most important evaluation with respect to kidney disease is the presence of hematuria. This is most commonly tested by using a dipstick for the presence of hemoglobin in the urine and by analysis of the microscopic sediment for erythrocytes. Erythrocytes and leukocytes are found in small numbers in normal urine. Exactly how these cells enter the urinary system is not known. Because the proportion of leukocytes to erythrocytes is much greater in urine than in blood, it is possible that the leukocytes come from diapedesis. The normal mean erythrocyte excretion is 29,000 cells per hour for females and 38,000 cells per hour for males. Leukocyte excretion is approximately 30,000 cells per hour with a maximum of about 100,000 cells per hour (Table 3). Screening the urine for hemoglobin is somewhat difficult because false-negative results for erythrocytes occur for various reasons with the dipstick methods. In a series of 1,000 patients, 35 of the 65 whose urine had erythrocytes in the sediment had a negative dipstick test. In a recent study in our laboratory of 708 urine specimens, 28 had greater than Grade 1 microscopic hematuria but only 15 had positive dipstick reactions; of the 126 with 1+ or greater dipstick reactions, only four had a negative microscopic reaction.

The orthotolidine reaction is sensitive to a hemoglobin concentration as low as 3 μg/liter, which is equivalent to 10 x 10^6 erythrocytes per liter or 10,000/ml. Normal urine may contain as many as 4,000 to 5,000 erythrocytes/ml; however, slight increases in the number of erythrocytes could result in a positive dipstick test. Hemoglobin and other oxidases including myoglobin catalyze the oxidation of orthotolidine to a blue product by oxygen released from hydrogen peroxide. When the urine is contaminated with a high bacterial content, it may give a false-positive reaction because of bacterial peroxidases or other oxidizing reagents. Of course, myoglobinuria must be ruled out as a cause for a positive dipstick reaction.

TABLE 3
Comparison of Addis Counts and Routine Examination of Sediment

Formed element	Addis count (total excretion/12 h)	Routine screening examination (no./HPF)
Casts	6,700-79,000	0 or 1-2
	122,000-1,000,000	1-2
	6,000,000-15,000,000	10-20
Erythrocytes	220,000-2,400,000	0-10
	2,500,000-8,200,000	1-20
	190,000,000-570,000,000	5-60
Leukocytes and epithelial cells	<1,000,000	0 (occ); 3-5 (usually)
	1,000,000-10,000,000	5-10
	10,000,000-75,000,000	10-20 (clumped)

(Modified from Kark RM, Lawrence JR, Pollack VE, Pirani CL, Muehrcke RC, Silva H: A Primer of Urinalysis. Second edition. New York, Harper & Row, Publishers, 1963. By permission.)

False-negative dipstick tests can occur in the presence of small numbers of erythrocytes if the cells do not lyse and release free hemoglobin. Ascorbic acid, when present in large amounts, decreases or inhibits the reaction of hemoglobin with the peroxide. Therefore, the dipstick should not be the only method used to test for erythrocytes, particularly in patients taking ascorbic acid or other reducing agents.

On the other hand, microscopic examination of the urine depends on having a urine that is not dilute and not very alkaline. Slight increases in erythrocytes may not be detected in the sediment. An erythrocyte content of about 60,000 cells/ml is needed for recognition of an increase on the microscopic examination. Probably it is best to perform both a dipstick test and a microscopic examination of the sediment in order to be sure of detecting hematuria.

The significance of hematuria cannot be overestimated. In the context of the clinical situation, with infection or obstruction and no other findings, one might regard hematuria as benign. However, the cause of the hematuria must always be considered. The presence of upper tract disease is most readily ascertained by noting erythrocyte casts in the urinary sediment. Common causes of microscopic hematuria, other than pathologic ones, include anticoagulant and aspirin-type drugs, and it seems reasonable to suggest that patients refrain from taking these drugs, if at all possible, prior to routine urinalysis.

Glucosuria

Glucosuria may imply renal disease, but it must be established that there is no abnormality in glucose metabolism. In practice this is done by comparing the plasma glucose value with the urinary glucose value and showing that the glucosuria is independent of hyperglycemia. The criteria set down by Marble[8] are stringent and are the most likely to separate abnormalities of glucose metabolism from renal impairment.

The most common way of measuring glucosuria is the glucose oxidase test. A major problem with this test is the false-negative reaction that is often seen in the presence of large amounts of ascorbic acid. Unfortunately, this is not easy to discern because ascorbic acid also causes false-positive reactions with an alternative method, Benedict's reagent for copper reduction. There are several other endogenous materials, including creatinine and uric acid, that may cause false-positive copper reduction and many drugs also will cause false-positive copper reduction reactions (Table 4). The glucose oxidase enzyme rarely gives a false-positive reaction, hypochlorite and peroxidases being the only things commonly encountered that cause such reactions.

TABLE 4
Interfering Substances in Tests for Glucosuria

Copper reduction tests:	
False-positive reactions—	
Ascorbic acid	Phenol*
Salicylates*	Turpentine
Cephalothin	Glucosamine
Creatinine	Streptomycin
Uric acid	Isoniazid
Penicillin	*p*-Aminosalicylic acid*
Ampicillin	Demethylchlortetracycline
Chloral hydrate*	Formaldehyde
Paraldehyde*	Aminopyrine*
Camphor	Nalidixic acid
Menthol*	
Enzyme tests:	
False-negative—	False-positive—
Ascorbic acid	Hypochlorite
Ketones	Peroxide

*Excreted as glucuronide, a reducing agent.

Normally, less than 1 g of glucose is excreted in the urine per 24 hours, but this varies somewhat depending on the metabolic status of the patient. Quantitative measurement of glucose excretion is not very helpful in assessing renal disease but is more appropriately concerned with such things as the management of diabetes and the regulation of insulin dosage.

Formed Elements

Examination of the urinary sediment is properly one of the most important aspects of the urinalysis. Unfortunately, this is often relegated to the least trained technician. Consequently, when a patient may have renal disease, most nephrologists and many other physicians examine the urinary sediment themselves. Multiple examinations may be very helpful in discovering abnormalities. Quantitative assessment of the urinary sediment has been somewhat difficult but has been attempted recently by Kark[9] by centrifuging an aliquot of urine through a Millipore filter and counting the different formed elements on the filter. This method has been used to screen large populations, and we are beginning to recognize that many patients have abnormal sediments with no appropriate explanation.

Many years ago it was recognized that hyaline and occasional granular casts, up to 5,000/day, are excreted in the urine (Table 3). On routine screening examination, this is 0 to 1 per high-

power field. An approximately 10-fold increase, up to 1 x 10^6 casts per 12 hours, is barely detectable. A count of 10 to 20 casts per high-power field indicates a 1,000-fold increase (6 to 15 x 10^6 casts per 12 hours). Unfortunately, the quantitative aspects of the urinary sediment have not been developed to the point that we can rely on the numerical value. The number of erythrocytes in the urine is 1 to 2 per high-power field in the normal male and up to 6 per high-power field in the normal female.

The presence of leukocytes in the sediment is often indicative of acute infection. However, many physicians have developed the habit of using antibiotics to treat patients with leukocytosis without clear evidence of infection. Moderate numbers of leukocytes and mixed leukocyte casts are seen in the urine of patients with subacute glomerulonephritis, lupus nephritis, or inflammatory disease of any type, such as interstitial nephritis from drugs and many other causes. Also, inflammatory interstitial disease in the bladder without infection, urethritis, prostatistis, or balanitis may lead to an increase in leukocytes in the urine. Conversely, leukocytes are rapidly lysed in hypotonic alkaline urine. Approximately 50% are lost in two to three hours at room temperature. This emphasizes the importance of prompt examination of the urinary sediment.

To evaluate the presence of infection, a Gram stain is extremely helpful on a properly collected urine specimen (clean-catch). We have shown in our laboratory that a Gram stain of an unspun sediment showing occasional bacteria per oil-immersion field indicates about 10,000 bacteria per ml; if there are bacteria in most fields, there are 100,000 bacteria per ml in the urine. Gram stains in our institution correlated with the urinary culture in 95% of cases when the Gram stain and culture were made from clean-catch urine specimens from females or specimens obtained by suprapubic puncture.

Renal cell casts are usually cylindric and vary in diameter depending on the size of the renal tubule or duct of their origin. The size is extremely important because the large, broad casts originate from the collecting duct and indicate that large sections of the kidney are not functioning properly. This usually means renal failure or large amounts of nonfunctioning tissue. Often, this type of broad cast is seen along with other inflammatory casts or erythrocyte casts. This type of sediment indicates a process that has different stages of development, such as in systemic lupus erythematosus, and is termed a "telescoped sediment."

Hyaline casts have no pathologic significance and are precipitates of Tamm-Horsfall protein. They are extremely abundant on examination under the phase-contrast microscope. Granular and coarsely granular casts are degenerated epithelial cell casts and indicate some degeneration of the tubular epithelium, which may or may not have significance depending on the status of the patient. Fatty casts or fat droplets in granular casts indicate increased cholesterol excretion and often are indicative of the nephrotic syndrome (but are not specific for it; they are seen in other circumstances such as diabetes and pregnancy). These fat droplets create the so-called Maltese cross forms when seen under polarized light; polarized light should be used to examine all sediments containing abnormal protein. Erythrocyte casts are the most specific finding in the urinary sediment; they indicate that erythrocytes are coming from the upper tract of the kidney. Erythrocytes may degenerate in alkaline urines or urines that have stood for any length of time and so must be sought diligently and repeatedly under appropriate circumstances. Erythrocyte casts that have degenerated to the extent that the erythrocytes themselves are not identifiable may tend to have a yellow or orange color. These may be confused with large urate-containing casts which tend to have a dusty red appearance.

Examination for crystals in the urine has been somewhat in disrepute for some time because most urine samples cool to 25°C on standing for a short period, and crystals precipitate out depending on the urinary pH. In acidic urine, amorphous urates, uric acid, calcium oxalate, and calcium carbonate crystals are seen; in alkaline urine, amorphous phosphates, triple phosphate, ammonium urate, and calcium phosphate crystals are seen. It is becoming apparent that patients who have renal lithiasis may have abnormal crystalluria. However, in order to detect abnormal crystals, the examination must be done with temperature and pH controlled. Under these circumstances, crystal analysis can become helpful in diagnosing the type of stone disease. There are some other crystals that can be identified and are always pathologic. Cystine in acidic urine is a colorless

refractile hexagonal plate; tyrosine and sulfonamide crystals are important to recognize.

Other Tests of Renal Function

Van Slyke defined renal clearance of a substance as that volume of blood that the kidney is able to clear of that substance per unit time. In the 1930's, Homer Smith and Harvey White established that the clearance rates of certain substances correlated with physiologic measurements of renal function: inulin clearance with the glomerular filtration rate and *p*-aminohippurate (PAH) clearance with renal plasma flow.

The interpretation of clearance depends on the knowledge of the mechanism of excretion of the substance in question. For example, inulin passes through the glomerular capillary walls but is not reabsorbed or secreted by the tubules; its filtration rate equals the plasma concentration times the glomerular filtration rate and, conversely, the glomerular filtration rate equals the excretion rate divided by the plasma concentration. Thus, the glomerular filtration rate of inulin equals the clearance of inulin. Unfortunately, there are no endogenous substances that have the exact clearance of inulin and therefore precise measurement of glomerular filtration is not possible from any known endogenous materials. The determination of the glomerular filtration rate requires either the infusion and maintenance of a constant plasma level of a substance such as inulin or the acceptance of approximations based on endogenous substances such as creatinine.

Creatinine is filtered at the glomerulus but also is secreted by the tubule. Therefore, the creatinine clearance is only an approximation of the glomerular filtration rate, especially in the near-normal range. Nevertheless, the creatinine clearance has been extensively used for the measurement of glomerular filtration rate and is the best substitute widely available.

In addition to the biologic problems that make the measured creatinine clearance higher than the actual clearance, the determination of creatinine is a colorimetric one which measures some noncreatinine chromogens. This tends to give a falsely low clearance value because these substances are not cleared into the urine at the same rate as creatinine. This error tends to balance the error of the secretory component of creatinine, and it has been thought that creatinine clearance approximates the glomerular filtration rate for most "clinical" circumstances. However, it has been amply demonstrated that the creatinine clearance may vary from the inulin clearance by as much as 100 to 200% in normal persons and by even more than this in abnormal circumstances. As renal function decreases, the component of secretion by the tubules tends to decrease and the proportion of true creatinine to total chromogens in the plasma tends to increase, which produces errors in opposite directions but in general tends to increase the creatinine clearance relative to the inulin clearance as the true glomerular filtration rate decreases until marked renal impairment intervenes.

A recent study in our hospital showed that 30% of the patients made significant errors in collecting 24-hour urine specimens. This has been obviated somewhat by attempting to perform short-term (two hours) clearances. However, problems of bladder emptying can produce significant errors in this short period unless extreme care is taken. To avoid having to collect urine, many have attempted to predict renal function merely from the serum creatinine level. In our laboratory the glomerular filtration rate as measured by inulin clearance was approximately equal to the value obtained by dividing the serum creatinine into 100 for men or into 80 for women. The error in the estimation was no more than that in the creatinine clearances themselves; that is, this estimate has an error of about 30% or 30 ml/min in near-normal clearances. This technique is least sensitive in the normal range. The serum concentrations may not change out of the normal range early in renal disease or the change may be within the error of the determination of the serum creatinine. The changes are so slight that alterations in renal function are difficult to determine with certainty. Although the serum creatinine value may in fact double as renal function decreases to half, it may still be within the normal range.

Nevertheless, as a measure of renal function, the serum creatinine value is still subject to less error than is the blood urea nitrogen or serum urea value that has been used for many years. The clearance of urea tends to be about 60% of that of inulin but is quite variable because it is markedly dependent on urine flow and protein intake and metabolism. Blood urea or blood urea nitrogen values are more appropriately reserved for assessment of protein metabolism in patients with renal impairment than for measurement of renal function.

Some of the problems of measuring inulin

clearances have been overcome by the recent use of appropriate materials tagged with a radioisotope, such as iothalamate labeled with ^{125}I; this has been shown to have a clearance similar to that of inulin. For those laboratories with the capability for measuring isotopes, this has resulted in saving of time for the determinations themselves. The major disadvantage of using inulin clearances, however, is the necessity for infusion of the inulin.

We have recently shown that [^{125}I] iothalamate can be injected subcutaneously so that the slow release from the depot provides a blood level constant enough for estimation of renal function accurately without infusion. The technique is to inject approximately 0.4 μCi/kg subcutaneously and then have the patient void at one-half hour and then again one and a half to two hours later. A blood sample is drawn at the beginning and the end of this time; plasma and urine radioactivities are counted and used to calculate the iothalamate clearance. Relative to the inulin clearance, the correlation coefficient with this technique is 0.998, and the standard deviation determination is about 6 ml/min (for the difference between the iothalamate clearance and the inulin clearance, the 95% confidence limit is 12 ml/min).

The measurement of renal plasma flow is important in patients with hypertensive disease, because renal plasma flow may decrease quite early compared to the glomerular filtration rate. However, there are no endogenous substances that measure renal plasma flow and it has not been a routine test of renal function.

Some substances such as *p*-aminohippurate (PAH) are almost completely removed from the blood as they pass through the kidneys. The rate of PAH excretion is therefore equal to the plasma concentration times the renal plasma flow, and PAH clearance is an excellent indicator of renal plasma flow as long as the plasma concentration does not exceed the secretory capacity of the tubule. Some radioactive substances have about the same clearance as PAH, such as ^{131}I-labeled iodohippurate (IOH). We have performed subcutaneous clearances with radioactive IOH and we have found that the clearance is about 20% lower than that of PAH, whether the IOH is given intravenously or subcutaneously. With a correction factor of 1.22, the IOH clearance approaches the PAH clearance. Unfortunately, the standard error for this determination is somewhat large, so that the error in determination of renal plasma flow using the subcutaneous technique is about 100 ml/min. A method for measuring renal function in clinical situations must be simple and have significantly increased accuracy over the serum creatinine or creatinine clearance to warrant its use. It is probable that the subcutaneous clearance of iothalamate or IOH could become useful in this regard.

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It's the Law

Hospital Alone Liable for Leaving Sponge in Patient

A surgeon performed gallbladder surgery on a patient in a hospital. The final sponge count was made by the hospital's nurse and was found to be correct. At a later operation, the laparotomy sponge was found to be the cause of the symptoms and was removed. Court found that the two nurses were involved in a joint activity in counting the sponges. The nurse was the hospital's employee and hence the hospital was found negligent. The patient was awarded $55,000.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Robinson v. St. John's Medical Center, Joplin, 508 S.W.2d 7 (Mo. Ct. of App., March 7, 1974.).
The Citation 29:9, August 15, 1974.

Acute Renal Failure

Pathology and Pathogenesis

JOHN T. CROSSON, M.D.* AND SULEYMAN GULMEN, D.D.S.*

Renal pathologic changes correlate poorly with the degree of physiologic impairment in patients with acute renal failure (ARF). The evidence against earlier etiologic theories, such as tubular obstruction and passive backflow, is convincing. Recent experiments have demonstrated preferential cortical ischemia in patients with ARF, suggesting altered hemodynamics due to increased vascular resistance. Morphologic changes in the kidney and the clinical renal failure are probably parallel results of the same underlying functional abnormality.

ACUTE RENAL FAILURE (ARF) is a clinical term denoting relatively abrupt failure of the kidneys to carry out their homeostatic functions, resulting in retention of nitrogen and the uremic syndrome. Two forms of ARF are now recognized clinically—the oliguric, with less than 400 cc. of urine in 24 hours and the non-oliguric, in which progressive azotemia is noted but with a normal or even slightly increased urine volume. No etiologic or pathologic differences have been demonstrated between these two forms of ARF.

Numerous clinical conditions[1,2,8] may predispose to the development of ARF (Table).

Historical Background

ARF did not gain wide recognition as a clinical entity until the early 1940's when Bywaters[3,4] reported many London air raid casualties suffering crush injuries developed ARF with a mortality rate of 90%. At autopsy these patients were found to have renal tubules filled with necrotic debris and casts.[4] Lucke[5] claimed the lesions in the crush syndrome were confined to the distal tubule, and the term "lower nephron nephrosis" became accepted until the classic studies of Oliver and his associates in 1951 changed this concept.[6]

Work of Oliver and His Group

These investigators, performing microdissection studies of individual nephrons, showed that the distribution of lesions in ARF is random, involv-

*Department of Pathology, Hennepin County Medical Center, Minneapolis, Minnesota.

TABLE
Etiology of Acute Renal Failure

- Extrarenal
  - Prerenal
  - Post renal
- Renal
  - I. "Acute Tubular Necrosis"
    - A. General:
      1. Trauma
      2. Hemorrhage
      3. Hypotension
      4. Post surgical
      5. Incompatible transfusions
      6. Burns
      7. Myoglobinuria
    - B. Toxic:
      1. Bichloride of mercury
      2. Carbon tetrachloride
      3. Ethylene glycol
      4. Antibiotics
      5. Analgesics
      6. Lead
      7. Iron
      8. Methanol
  - II. Renal Cortical Necrosis
  - III. Acute Renal Artery or Vein Occlusions
  - IV. Glomerular
    - A. Acute diffuse proliferative glomerulonephritis
      1. Post infections
      2. Rapidly progressive
      3. Lupus erythematosus
    - B. Thrombotic microangiopathy
      1. Hemolytic uremic syndrome
      2. Thrombotic thrombocytopenic purpura
      3. Post partum renal failure
    - C. Focal, segmental glomerulonephritis
      1. Vasculitis
      2. Wegeners granulomatosis
      3. Henoch-Schönlein purpura
  - V. Intrarenal Artery and Arterioles
    - A. Malignant hypertension
    - B. Polyarteritis nodosa
    - C. Progressive systemic sclerosis

ing proximal as well as distal tubules,[6] refuting the concept implied by the term "lower nephron nephrosis". Acute tubular necrosis (ATN) has largely supplanted the term "lower nephron nephrosis".

Oliver defined two relatively distinct pathologic lesions. The first, correlating with ischemic etiologies and called tubulorrhexis by Oliver, is characterized by destruction of both the tubular epithelial cells and the basement membrane.[6] This lesion is most pronounced in the proximal convoluted tubule at the cortical medullary junction and in the distal convoluted tubule, although lesions may be found anywhere along the nephron. He emphasized that not all nephrons are affected even in severely damaged kidneys.[6] In contrast, the nephrotoxic lesion which results from the action of toxins on the renal epithelium, is characterized by uniform necrosis of the proximal tubular epithelium but with preservation of the basement membrane. This lesion is confined to the proximal tubule with a uniform distribution among the nephron population. Although described as separate lesions, they may in fact be found simultaneously.[6] Of the two, the prognosis for restoration of function is best with the nephrotoxic lesion since the basement membrane is spared and serves as a scaffold for regenerating epithelium.

Early investigators of the histopathology found in ARF attempted to correlate morphologic changes with loss of renal function. However, Finckh evaluated the morphology in 28 fatal cases of ARF and concluded that structural changes are not the cause of the oliguria.[7] The pathologic alterations in ATN and cortical necrosis will be discussed. The other entities included in the Table, however, are beyond the scope of this paper, but reviews may be found in several recent monografts.[8,9]

Grossly, kidneys with ATN are swollen with pale cortices and congested medullae. Microscopically, the glomeruli are normal unless there is preexisting glomerular disease. Occasionally the cells lining Bowman's capsule become tall and resemble tubular epithelial cells. The cell changes vary with the interval between acute insult and biopsy. Tubular involvement is characteristically patchy. Necrosis of tubular epithelium may be seen early after the insult but it is not common. Both proximal and distal tubules may have dilatation, vacuolization of the epithelial cells, free

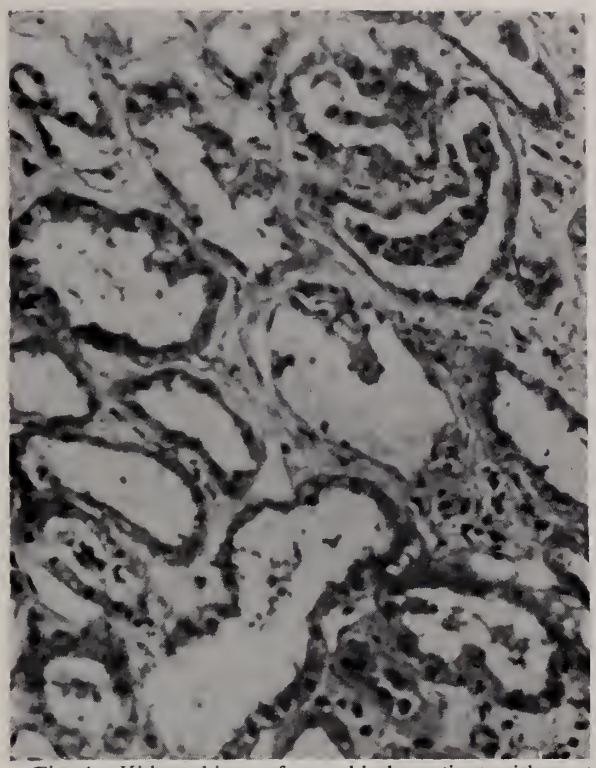


Fig. 1—Kidney biopsy from elderly patient with post surgical ATN, showing epithelial cells free in tubular lumen and adjacent tubule denuded of epithelium. H & E X325.

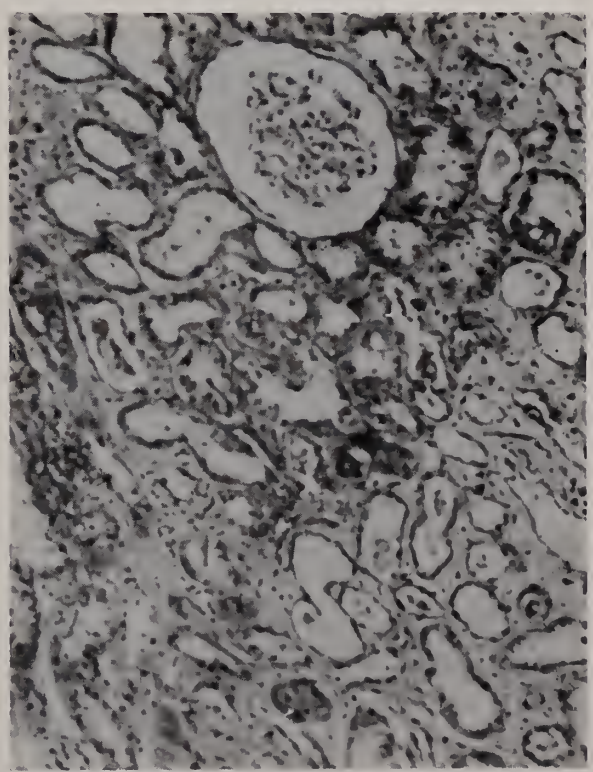


Fig. 2—Same case as Figure 1. Note normal glomerulus, tubular dilatation, flattened epithelium lining some tubules and interstitial edema. H & E X200.

epithelial cells within the lumen (Figure 1), and flattened epithelial cells (Figure 2). The latter cells, which may demonstrate increased basophilia, deeply staining nuclei, and mitotic figures, probably represent regenerated epithelial cells. It is impossible from a single histologic section to decide whether a tubule lined with flattened epithelium is proximal or distal. Though difficult to demonstrate, disruption of the tubular basement membrane may also be seen (Figure 3).[9]

The presence of casts may be striking. This was one of the first abnormalities to catch the eye of early workers. Usually they are present in the distal convoluted tubules and the collecting ducts. Casts may be eosinophilic and homogenous, eosinophilic and granular, or brownish in color. When brown they usually stain positive with benzidine.

The interstitium characteristically demonstrates edema and infiltration with inflammatory cells which may include polymorphonuclear leukocytes, mononuclear cells (Figure 3), and occasionally a large number of eosinophils.[9] When complete recovery does not occur, interstitial fibrosis ensues. Fortunately, nearly normal renal histology and function return in most patients surviving an episode of ATN.[10]

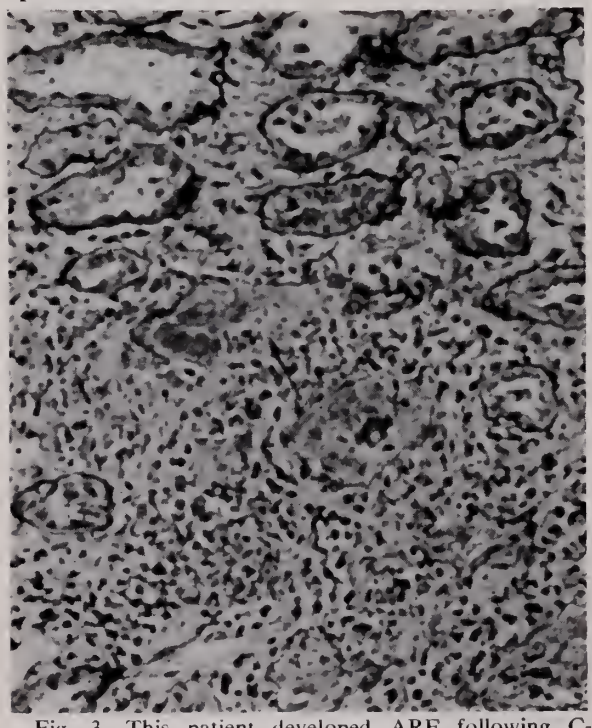


Fig. 3—This patient developed ARF following C-section. Arrow points to disrupted tubular basement membrane. Adjacent tubular lumen is filled with necrotic debris. Note interstitial cellular infiltrate. H & E X325.

Electron microscopy is of limited value in the study of ATN. Mitochondrial swelling as well as disintegration of cristae have been described. Occasionally in renal biopsies separation of the tubular epithelium from the basement can be noted. Disruption of basement membranes is rare. Loss of microvilli is probably non-specific.

Cortical necrosis, a morphologically distinct lesion, was the cause of 2% of the cases of ARF in a large series.[11] It is most frequently a complication of pregnancy, usually abruptio placentae, but is also associated with toxemia, sepsis, burns, and shock. Histologically, cortical necrosis differs from ATN. Complete necrosis of the entire parenchyma in a region including glomeruli, interstitium and tubules may occur. Calcification is common. Cortical necrosis may be widespread or focal. Even when widespread, the outer rim of the cortex as well as the cortical medullary junction tends to be spared. These findings explain the occasional clinical recovery after cortical necrosis.[12] Spasm of intermediate size arteries and a Schwartzman reaction have been proposed as causes of cortical necrosis.[9]

The pathogenesis of ATN is not known. The morphologic findings, particularly in "crush syndrome" suggested to early workers that oliguria might be due to obstruction of tubular flow by casts or by necrotic debris. Others have postulated tubular compression by interstitial edema. Such obstruction should result in increased intraluminal pressure thereby lowering effective glomerular filtration pressure and causing decreased glomerular filtration. Micropuncture studies performed by Oken and co-workers in rats with both mercury induced and glycerol induced hemoglobinuric renal failure have demonstrated a significant *decrease* in intratubular hydrostatic pressure rather than an increase.[13,14] The decrease was noted within 15 minutes after the insult, simultaneously with the onset of decreased glomerular filtration. Furthermore, these authors noted that casts and debris which lodged in tubules could be moved along the tubule with injection of saline at pressures equal to or below normal physiologic intratubular hydrostatic pressure.[14]

In another study, using rats with methemoglobin induced ARF, decreased pressure in the proximal tubules as well as in the afferent glomerular vessels was noted.[15] Furthermore, measurements of renal interstitial pressure based on renal vein

wedge pressure in oliguric patients have generally shown no abnormalities. These studies and the consistent failure to find casts in a high percentage of nephrons in patients with ARF, have led most observers to regard tubular obstruction as a contributory rather than a primary cause of ARF.

Based on the observations of Oliver that the tubulorrhexie lesions consists of necrosis of both epithelial cells and basement membranes,[6] some workers have postulated passive backflow of glomerular filtrate through such ruptured tubules. However, a number of studies contradict this theory. In the micropuncture studies by Oken and co-workers, saline was suspended between two oil droplets within a ruptured tubule, and reabsorption was not found.[13] This finding is supported by Flamenbaum. He demonstrated no difference in single nephron glomerular filtration rates measured along the entire length of proximal tubules in rats with mercury induced ARF, which strongly suggests that fluid could not be leaking out of the tubules.[16] Furthermore, dogs with uranyl nitrate induced renal failure develop rapidly severe depression of both inulin clearance and total renal blood flow before histologic alterations in tubules appear.[17] These experiments indicate that passive backflow is not a significant factor in the pathogenesis of ARF.

Failure to demonstrate an organic etiology for ARF has led to a search for a functional abnormality. Recent evidence points to a marked alteration in renal hemodynamics as the basic mechanism in most cases of ARF. Hollenberg and co-workers,[18] in studying 20 patients with oliguric ARF due to varying causes, found marked preferential renal cortical ischemia.[18] In xenon washout studies they demonstrated the absence of an early rapid component which represents cortical blood flow. Other evidence included the consistent failure to demonstrate the cortical microvasculature angiographically, and the lack of bleeding from the renal cortex at open biopsy. A decrease in cortical blood flow using xenon washout has also been found by Flamenbaum in uranyl nitrate induced renal failure in the dog three hours after administration of the toxic agent.[17] The total renal blood flow was decreased, the outer medullary flow was increased, and the glomerular filtration, as measured by inulin clearance, was reduced to 25% of normal. As further confirmation of selective cortical ischemia, there was a marked decrease in cortical deposition of Sr^{85} labelled microspheres (15 microns) within 6 hours after uranyl nitrate administration. Finally, autoradiographs of kidneys using $krypton^{85}$ demonstrated absence of perfusion in many areas of the cortex.[17]

These data suggest that altered renal hemodynamics are crucial in the development of ARF and result from increased renal vascular resistance. The location of increased resistance is still disputed. The "no reflow theory", in which the circulation fails to return to the parenchyma of various organs after graded periods of ischemia, suggests an obstruction in the glomerular capillaries, secondary to ischemic swelling of endothelial cells and trapping of poorly deformable red cells in the narrowed lumina. Summers and Jamison,[19] in implicating the red cell, demonstrated no flow of 600 Å carbon particles in rat kidneys following 60 minutes of ischemia, but when the kidneys were flushed with isotonic saline to remove the blood, carbon perfusion became normal. Furthermore, rigid red cell ghosts (calcium treated) prevented carbon perfusion while pliable red cell ghosts (water treated) failed to prevent perfusion of carbon particles.[19] Flores and co-workers[20] have recently suggested that the endothelial cells may swell and contribute to the no reflow phenomenon along with the red cell. They demonstrated a two fold increase in the thickness of endothelial cells lining renal capillaries following 60 minutes of ischemia by using planimetry on electron micrographs. Swelling of interstitial cells was also noted. The cellular swelling and hemodynamic abnormalities were both corrected by hypertonic mannitol.[20]

Other investigators postulate the site of increased vascular resistance to be preglomerular, probably in the afferent arteriole. The renin-angiotensin system has been implicated in this theory on the basis of several findings. For example, Goormaghtigh in 1945 noted distinct hypertrophy of the juxtaglomerular apparatus in patients with renal failure from the crush syndrome.[21] Subsequently, numerous investigators have observed elevated plasma renin levels in patients with ARF.[22,23,24] Flamenbaum also noted increased plasma renin levels in dogs with uranyl nitrate induced ARF.[17] Further support for the role of the renin-angiotensin system comes from the

studies of McDonald and co-workers who demonstrated that dietary saline loading of rats for two months protected them from developing hemoglobinuric ARF after intramuscular injection of glycerol.[25] Saline loading has been shown to deplete the kidney of renin and to result in low peripheral blood renin levels. With the variables of blood volume, urinary osmolality, urine sodium and plasma sodium concentration controlled, the authors concluded that protection from ARF was due to renal renin depletion.[25] Saline loading also has been shown to protect against mercury induced ARF.[26]

Short term administration of saline which reduces peripheral renin levels but not renal renin levels, however, does not protect against glycerol induced ARF.[27] Likewise, active immunization against renin decreases plasma renin levels without affecting renal renin levels and is not protective against either mercuric chloride or glycerol induced ARF in the rat.[28] This suggests that renin most likely acts in the kidney rather than peripherally. Passive immunization against angiotensin II, which can produce selective cortical ischemia when infused into the renal artery,[29] did, however, protect against glycerol induced ARF in the rat.[30] In these animals, interestingly enough, the same morphologic changes of ATN developed in the protected animals as well as in the controls. These results show the lack of correlation between morphologic changes and functional abnormalities.

The mechanism of intrarenal renin release in ARF is unknown. There is evidence for a receptor in the wall of the afferent arteriole which probably responds to changes in wall tension by stimulating renin release.[31] A less well defined sodium sensitive receptor appears to be present in the macula densa of the distal convoluted tubule.[31] Thurau has some evidence that increased sodium concentration of the glomerular filtrate at this level of the nephron results in increased renin secretion.[32,33] This sodium sensitive receptor may be responding to something more complex than just sodium concentration.[31] It is clear, though, that the macula densa responds in some way to an altered sodium load by stimulating renin release. DiBona, however, has been unable to confirm a relationship between distal tubular sodium concentration or sodium load, plasma renin concentration, and severity of ARF in glycerol treated rats.[34]

Flamenbaum has recently proposed that in ARF the initiating event damages tubular function, resulting in altered tubular handling of sodium and water.[35] The altered composition of the glomerular filtrate in some way stimulates local release of renin, which, along with converting enzyme in the juxtaglomerular apparatus,[36] leads to local production of angiotensin II. Marked afferent arteriolar vasoconstriction occurs in the presence of angiotensin II. This increased arteriolar resistance is thought to cause the preferential cortical ischemia, decreased glomerular filtration, and azotemia seen in ARF.[35]

Summary

None of the morphologic abnormalities collectively known as Acute Tubular Necrosis can be correlated with the development of Acute Renal Failure. The evidence against the theories of tubular obstruction and of passive backflow is convincing. Recent data which definitely demonstrate preferential renal cortical ischemia, favor a functional abnormality, probably increased vascular resistance. This increased resistance may either be in the glomerular capillaries or may be preglomerular in the afferent arterioles. Some evidence implicates the renin-angiotensin system. The histologic changes and the clinical renal failure are probably parallel results of the same functional abnormality and do not have a cause and effect relationship as previously thought.

Acknowledgment

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9-36. Will be found on page 87.

Acute Tubular Necrosis (Vasomotor Nephropathy)

Review of Clinical Aspects and Report of Five Cases Due to Trauma

DONALD A. DUNCAN, M.D.*

Many of the clinical characteristics of acute renal failure due to ischemic injury are discussed. Prerenal failure must be differentiated from the oliguric and non-oliguric forms of acute tubular necrosis. Conservative management, the value of early and frequent dialysis, duration of oliguria, mortality and the prognosis for survivors of acute tubular necrosis are reviewed. Elderly individuals with renal failure following surgery or trauma have the poorest prognosis.

THE PRESENT REPORT will review clinical aspects of acute renal failure due to ischemic injury. Such terms as acute tubular necrosis, tubulointerstitial nephropathy, shock kidney, crush syndrome, burn nephritis and lower nephron nephrosis have been applied. Today many nephrologists prefer the term "vasomotor nephropathy"[1] to emphasize the hemodynamic changes that produce nearly complete cessation of glomerular filtration prior to any histopathologic alterations. Differentiation from acute glomerulonephritis, bilateral cortical necrosis or a drug-induced acute interstitial nephritis may be impossible without renal biopsy.

Oliguria, often defined as a urine volume of 20 ml/hr (480 ml/day) or less, is the most easily recognized sign of acute renal failure. Yet, it must be remembered that oliguria can be physiologic. Merrill[2] has noted that a person with normal kidneys eating an average diet may, by restricting fluids, produce a urine volume of 400 ml/24 hrs with a specific gravity of 1.030 or above and an osmolality over 1200 mOsm/kg. If sodium and protein are omitted from the diet and fluid intake is limited, as may occur during intravenous therapy, a 24-hour volume of 300 to 500 ml with specific gravity 1.008 to 1.014 may be produced. However, in the usual clinical setting oliguria with isosthenuria indicates renal failure.

Conversely, acute renal failure with progressive azotemia may occur without oliguria[3] or even in association with polyuria.[4] Acute polyuric renal failure with urine volumes of 3000 to 5000 ml daily has been described following methoxyflurane (Penthrane®) anesthesia.[4] The renal tubule is unable to respond to vasopressin.

Diagnosis of Acute Renal Failure

Initially, cardiovascular insufficiency due to any cause will produce a small volume of concentrated urine. This state of prerenal failure, if severe, will lead to ischemic renal parenchymal injury if not corrected rapidly. The oliguria of prerenal failure has the following characteristics:

1. High urine osmolality and specific gravity. The urine osmolality: plasma osmolality ratio is greater than 1.5.
2. Urea, the primary solute in the urine, often is present in a concentration of 3000 mg/100 ml or more. The ratio of urine urea nitrogen to blood urea nitrogen (UUN:BUN) is greater than 20.
3. Urine sodium concentration is less than 20 mEq/L as a result of nearly complete tubular reabsorption of sodium.
4. Increased urine volume and correction of azotemia with restoration of blood volume, blood pressure and total body hydration, either alone or in combination with administration of diuretics. The latter may be necessary in the presence of increased production of antidiuretic hormone.

Once acute renal failure has become established the small volume of urine elaborated usually has the following characteristics:

1. Urine osmolality is approximately 400 mOsm/kg or less, or ratio of urine to plasma osmolality less than 1.5.

*Clinical Assistant Professor, Department of Medicine, University of Minnesota, Minneapolis, and Staff Member, St. Louis Park Medical Center, Minneapolis, Minnesota.

2. The UUN:BUN ratio is less than 10, often less than five.
3. Urine sodium concentration rises to 40-90 mEq/L as a result of impaired tubular reabsorption of sodium. The urine potassium concentration falls.
4. No response to correction of cardiovascular insufficiency plus administration of a trial fluid load of 1000 to 1500 ml electrolyte solution.
5. No or incomplete response to diuretics. At best, diuretics will convert the oliguric state to one of non-oliguric renal failure, making fluid and nutritional management easier. Azotemia will progress, but possibly at a reduced rate.

The rate of rise of blood urea nitrogen will not differentiate prerenal failure from acute tubular necrosis. In fact, azotemia may occur post-operatively, for example, if septicemia, absorption of blood clot, or gastrointestinal bleeding occurs despite normal renal function.

Progression from early prerenal failure to advanced parenchymal injury (acute tubular necrosis or vasomotor nephropathy) is a continuum. Thus the two categories may not be as distinct as suggested by the above criteria. Also, post-renal failure (obstructive uropathy) and chronic renal failure must be excluded before the above rules are applied. During recovery from acute tubular necrosis the urinary sodium concentration progressively falls as the potassium concentration rises due to reabsorption of sodium in exchange for potassium in the distal tubule.

During the early stages of acute glomerulonephritis with oliguria the urine specific gravity is high, sodium concentration low, and urea concentration high, compatible with impaired glomerular filtration but good tubular function.[5] The renal failure of advanced Laennec's cirrhosis also is characterized by a very low urine sodium concentration, often less than 10 mEq/L.

Non-oliguric Renal Failure

During recent years non-oliguric acute renal failure following ischemic injury to the kidney has been recognized with increasing frequency. Histologically the oliguric and non-oliguric forms are similar, the difference being the degree of impairment of renal hemodynamics. One hazard of non-oliguric renal failure is that it will not be recognized. Although the urine volume is relatively good, eg, 1200 ml/24 hrs, administration of 2000 to 3000 ml of fluid daily can result in pulmonary edema.

Non-oliguric renal failure resembles the early diuretic phase of the oliguric variety. Urine volume is good but azotemia increases. In most patients with non-oliguric failure the urine sodium concentration is low from the beginning and remains low.[3] Thus a low urine sodium helps to exclude parenchymal injury only when oliguria is present. The degree of uremia often is not severe enough to require dialysis. Hyperkalemia usually is mild, but death from hyperkalemia can occur if exogenous sources of potassium such as old bank blood, K+—penicillin, K+—containing I.V. fluids, etc., are not monitored.

In non-oliguric, as well as oliguric failure, the ratio of urine urea to blood urea nitrogen is less than 10.[3]

Diuretics

It seems well established that when mannitol is given to animals *prior* to a renal insult, or to patients *during* surgical procedures such as abdominal aortic aneurysmectomy, acute renal failure can be prevented. The mannitol increases plasma volume, renal blood flow, glomerular filtration and intratubular pressure. When given *after* the renal insult, results are less dramatic. Barry[6] has emphasized that between the period of prerenal failure ("functional failure") and development of established renal failure ("organic failure") there is a period of time, usually less than 48 hours, when the intravenous administration of mannitol can produce variable degrees of renal functional recovery. He recommends giving mannitol as a hypertonic solution, usually 25 gm, immediately upon recognition of oliguria, rather than waiting to see if the administration of blood, plasma or electrolyte solutions alone will produce a diuresis.

Flores, Leaf, et al.[7] may have explained, at least in part, the mechanism by which mannitol prevents acute tubular necrosis. Working with animals, they demonstrated that transient occlusion of the renal artery produces cellular swelling with subsequent obstruction of vessels at the capillary level. It is believed that ischemia impairs cell metabolism, allowing sodium to enter passively, followed by water. Because of the cellular swelling and capillary obstruction "no-reflow" occurs when the renal artery is unclamped. These investigators found that isosmotic expansion of extracellular fluid volume by administration of isotonic saline could not prevent or correct the problem of no-reflow, but administration of hypertonic mannitol did. The increased extra-cellular osmo-

tality removed fluid from the cell, decreased swelling and relieved small vessel obstruction. The administration of mannitol can be effective only when given before the ischemic injury produces cell death.

The more potent "loop" diuretics may initiate a diuresis during the early stages of acute parenchymal renal failure when mannitol will not. Furosemide is preferred to ethacrynic acid because of the much greater ototoxicity of the latter. Large doses may be necessary. A convenient schedule is to give an initial 80 mg of furosemide intravenously, then double the dose every two hours, depending on the response, to a total of 1200 mg. If little or no response has occurred by this time it is unlikely that larger doses will produce a significant diuresis, but amounts as high as 6000 mg have been given during a 24 hour period. In addition to inhibiting the tubular reabsorption of sodium there is evidence that furosemide (and ethacrynic acid) increases renal cortical blood flow.[8]

Ototoxicity from furosemide usually is transient and appears to depend on the dose and rapidity of intravenous administration. Large doses (over 300 mg) should be infused over a 15-60 minute period.

In practice mannitol and furosemide can be given together, but mannitol should be given priority if it appears that the plasma volume is decreased. Furosemide is the diuretic of choice if the patient is significantly overhydrated, especially if pulmonary edema is present.

Conservative Management of Acute Renal Failure

Once it is established that a diuresis cannot be induced and obstructive uropathy has been excluded by cystoscopy and retrograde pyelography, the usual principles of conservative management must be applied.[9] The average 70 kg adult requires 400 ml of fluid daily plus replacement of all measured losses. When caloric intake is inadequate, as it often is, a daily weight loss of one-half to one pound should occur. If factors contributing to a catabolic state such as high fever, sepsis, multiple surgical procedures, or administration of antianabolic drugs are present, an even greater weight loss may take place. Failure to lose weight indicates progressive overhydration. A minimum of 100 gm of glucose or other carbohydrate should be given daily to decrease ketosis and endogenous protein catabolism. Anabolic drugs may be beneficial if the rate of catabolism is not high. Hyperkalemia and its cardiotoxicity usually can be controlled by the administration of glucose, insulin, calcium, sodium bicarbonate and polystyrene sulfonate (Kayexylate®). The latter often is given with a 70% solution of sorbitol to produce an osmotic catharsis resulting in the loss of water and potassium.[10] Antacids containing magnesium should be avoided.

McCracken[11] demonstrated that a diet consisting of 20 gm of high biologic value protein (three eggs) can be given daily without increasing the rate of urea production. Presumably this amount spares the breakdown of a similar amount of endogenous protein. Thirty grams of protein daily increases azotemia.

Abel et al.[12] found that the addition of the eight essential amino acids to an intravenous hypertonic glucose solution decreased the rate of rise of blood urea, lowered serum concentrations of magnesium, phosphorus and potassium and delayed or occasionally eliminated the need for dialysis. In contrast, administration of casein hydrolysate, containing non-essential amino acids and used in most hospital hyperalimentation solutions, did not slow the progression of azotemia. This is in keeping with the work of Giordano[13] and Giovannetti and Maggiore[14] who demonstrated that the administration of essential amino acids with a high caloric source (glucose) leads to the recycling of urea nitrogen with subsequent incorporation into non-essential amino acids to form new tissue protein. This anabolic effect leads to tissue incorporation of magnesium, potassium and phosphorus.

Drugs that depend on the kidney for excretion should be avoided or given in reduced dosage. Examples are the aminoglycoside antibiotics and the polymixins.

When to Dialyze

The initial prognosis of the patient with acute tubular necrosis due to trauma or surgery depends on extra-renal factors. The subsequent prognosis often depends on the control of uremia-related factors such as hemorrhage and infection. Merrill[15] has stated that when treating acute renal failure dialysis "should be utilized prophylactically—that is, to prevent the complications of uremia rather than to treat them after they have become manifest." Teschan[16] first demonstrated the value of prophylactic daily dialysis, allowing a more liberal protein intake and presumably better wound healing. Prior to December 1958 Scribner[17] dialyzed patients only when they were clinically

uremic. Thirty-one percent of 42 patients survived. After December 1958 patients were dialyzed frequently enough to keep the blood urea nitrogen under 120 mg/100 ml. Seventy-four percent of 61 patients survived. Before July 1, 1968, Kleinknecht et al.[18] had a mortality of 43% in 173 patients dialyzed only when the blood urea exceeded 350 mg/100 ml (BUN 163 mg/100 ml) or severe electrolyte imbalance was present. Subsequently patients were dialyzed to keep the blood urea under 200 mg/100 ml (BUN 93). The mortality fell to 29% in 147 patients. Schreiner[19] has recommended dialyzing patients with crushing injuries daily if necessary to keep the blood urea nitrogen under 100 mg/100 ml.

The series of Scribner and Kleinknecht included all causes of acute renal failure. Unfortunately, they are not controlled studies. Concurrent or alternate case studies are not available.

There is evidence that a high serum concentration of urea itself contributes to the bleeding diathesis of uremia.[20,21] Kleinknecht[18] found that in acute renal failure early and frequent dialysis reduced the frequency of hemorrhage from 26 to 18% and deaths from hemorrhage from 14 to 5%. The incidence of septicemia was not decreased but deaths from septicemia fell from 14 to 6%. Other investigators have documented that early and frequent dialysis decreases the frequency of hemorrhage, but its ability to reduce mortality from infection is less well established.[18]

Today most patients with acute renal failure are started on dialysis when the blood urea nitrogen reaches 100 mg/100 ml or the serum creatinine reaches 10 mg/100 ml. They then are dialyzed frequently enough to avoid exceeding these limits. Avoiding dialysis because the urine volume is beginning to rise can be disastrous. As shown in the subsequent case reports, many days may elapse before azotemia stops progressing. Often one can safely delay dialysis longer in the patient with acute renal failure due to "medical" causes—transfusion reaction, CCl_4 intoxication, etc.—where the catabolic rate is low, than in the traumatized or post-surgical patient.

Case Reports

Five male patients, ranging in age from 17 to 30 years, were transferred to the Methodist Hospital (Minneapolis, Minnesota) Artificial Kidney Center between 1967 and 1971 with acute oliguric renal failure due to crushing injuries. Four were involved in automobile accidents, the fifth overturned a tractor on himself. All were in shock initially and were resuscitated with variable amounts of whole blood, plasma (or 5% plasma protein fraction) and electrolyte solutions. No diuresis occurred when diuretics were given.

The patients' injuries are listed in Table 1. The clinical course for Cases 2 and 3 during the oliguric and diuretic phases of their illness is shown in Figures 1 and 2. Cases 3 and 5 received 157 and 122 units of blood respectively. Their courses were complicated by disseminated intravascular coagulation.

Four of the five survived. Extensive pulmonary injuries complicated by pneumonia resulted in the death of Case 4 after 15 days. Cases 1 and 2 recovered without any significant disability. Case 3 recovered fully except for the loss of the left leg. Case 5 lost the left leg, lost the vision in his right eye due to a panophthalmitis and became deaf, probably due to the administration of gentamicin and kanamycin for recurrent abscesses and septicemia due to Gram (−) bacilli including *Pseudomonas aeruginosa.*

For the survivors the period of oliguria (urine volume less than 480 ml/24 hrs) ranged from 12 to 41 days (Table 2). Even after the urine volume reached 1000 ml/24 hrs an additional four to six days elapsed before renal function was adequate to decrease the blood urea nitrogen without additional dialysis. Because of the hypercatabolism, daily or alternate day dialyses were

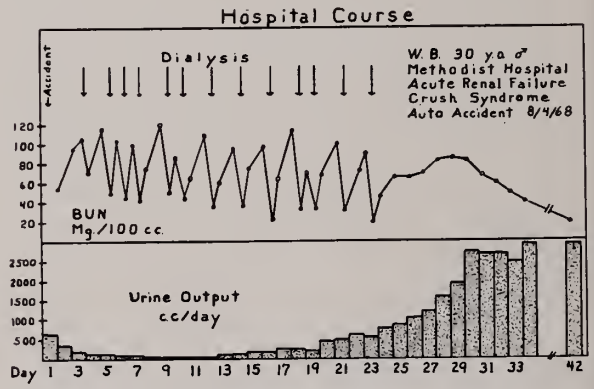


Fig. 1—(Case 2)—Hospital course of patient W. B. from onset of acute renal failure to recovery from uremia.

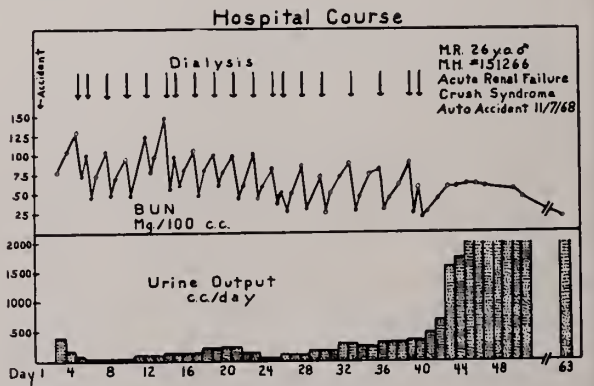


Fig. 2—(Case 3)—Hospital course of patient M.R. Urine volume less than 480 ml/24 hrs for 41 days, followed by a rapid diuresis.

TABLE 1
Injuries Sustained

Case No.	Age Yrs.	Nature of Accident	Injuries
1	17	Auto	Right pneumothorax & pulmonary contusion Bilateral humeral fractures Dislocation right hip Multiple rib fractures Lacerations of liver
2	30	Auto	Multiple rib fractures Bilateral pneumothorax Cerebral concussion Fracture left radius & ulna Compound fracture left tibia & fibula Fat embolism with coma & apnea 3 days
3	26	Auto	Fractures left forearm, femur, fibula & foot Pelvic fractures Rupture left femoral artery & vein
4	22	Auto	Multiple rib fractures, flail chest Right pulmonary contusion & pneumothorax Cerebral concussion Lacerations of liver
5	19	Tractor	Multiple pelvic fractures Rupture of urethra Occlusion left iliac artery 3° burns of legs & pelvis

TABLE 2
Period of Oliguria in Five Cases of Acute Tubular Necrosis after Crushing Injuries

Case No.	Days of Oliguria: Urine Vol less than 480 ml/24 hrs	Days of Oliguria: Urine Vol less than 1000 ml/24 hrs	Day Blood Urea Nitrogen Fell Without Dialysis	No. of Dialyses	Serum K+ Before First Dialysis mEq/L
1	12	18	22	6	6.1
2	21	25	31	13	5.9
3	41	42	47	19	6.1
4	15	15	—	7	5.7
5	18	19	24	12	8.8

TABLE 3
Recovery of Renal Function

Case No.	Months after Initial Injury	Blood Urea Nitrogen mg/100 ml	Serum Creatinine mg/100 ml	Creatinine Clearance ml/min/1.73 m^2	Urine Specific Gravity after 15 Hrs Fluid Deprivation
1	12	8	1.0	110	1.022
2	6	10	1.2	99	1.020
3	10	20	1.1	109	1.026
4	10	10	0.8	93	1.018

required to keep the blood urea nitrogen from exceeding the range of 100 to 125 mg/100 ml. The number of dialyses of six to eight hours each that was required are shown in Table 2. All dialyses were performed with the Travenol RSP artificial kidney using the Ultra-Flo 145 coil* and regional heparinization. Hyperkalemia was well controlled by conservative means prior to initiation of dialysis in Cases 1 to 4. These same measures were not applied as vigorously as they should have been in Case 5.

The recovery of renal function in the four survivors was excellent as shown in Table 3. Urinalysis became normal in all. Creatinine clearance ranged from 93 to 110 ml/min/1.73m^2.

Duration of Oliguria

Forty-one days of oliguria (Case 3) is unusually long. Most patients with acute tubular necrosis enter the diuretic phase after one to three weeks. Periods of oliguria of 35 and 40 days following crushing injuries with subsequent good recovery of renal function have been reported.[18,22] Merrill mentions recovery after as long as 47 days but does not give the etiology of the acute renal failure.[23] Siegler[24] reported a case of oliguria of 72 days duration due to a combination of severe dehydration and apparent gentamicin toxicity before diuresis occurred. Oliguria lasting 50 and 53 days with subsequent diuresis has been reported following ingestion of ethylene glycol.[25,26] Subsequent renal function was severely compromised due to interstitial fibrosis associated with deposition of calcium oxalate crystals.

Depending upon the clinical circumstances a renal biopsy may be indicated after approximately three weeks, or sometimes sooner, to look for other causes of acute renal failure such as bilateral cortical necrosis or acute glomerulonephritis.

Mortality

The mortality from acute tubular necrosis following trauma, burns and surgery remains discouragingly high. For World War II (dialysis not available) it was 91%.[27] During the Korean conflict it fell to 53% (68% for those requiring dialysis), and during the Vietnam War 69% at 3rd Field Army Hospital and 63% at Clark USAF Hospital.[27] Comparing Vietnam to Korean War results is misleading, however, because with better initial care of the wounded during the Vietnam conflict renal failure occurred less frequently, probably only in the more severely injured. Such individuals would be more likely to succumb to their non-renal injuries regardless of how well the renal failure was handled. The incidence of renal failure was 1:200 hospitalized wounded in the Korean War and 1:600-700 in the Vietnam War.[27]

In civilian practice the mortality from acute tubular necrosis requiring dialysis following trauma and/or surgery averaged 64% in six series published before 1965.[27] Mortality from medical causes of acute renal failure was 40%. In a recent report from the Mayo Clinic[28] the mortality for acute renal failure requiring hemodialysis was as follows:

47% of 88 post-surgical patients
72% of 18 post-trauma patients
21% of 14 obstetric patients.

In the series of Kleinknecht et al.[18] the mortality rate was as follows:

38% of 62 post-surgical patients
33% of 12 post-trauma patients
6% of 30 post-abortion patients.

It is easy to understand why the two most common complications of uremia, hemorrhage and infection, more frequently lead to a fatal outcome in the injured or post-surgical patient.

Age is an important determinant of mortality. Brown et al.[29] noted a mortality rate of 73% in 26 patients over the age of 60 with post-surgical acute renal failure, as compared to a 50 to 58% mortality in younger age groups.

Prognosis for Survivors of Acute Tubular Necrosis

The disruptive ischemic tubular lesions noted by Oliver[30] during his microdissection studies and the permanent interstitial histologic alterations observed by Muehrcke[31] suggest that functional recovery from acute tubular necrosis may not always be complete. Indeed, this is the case. Finkenstaedt and Merrill[32] found that most patients followed up to six years after recovery from acute tubular necrosis had inulin clearances that stabilized between 60 and 90% of normal.

One of the more informative studies of the long-term prognosis of survivors from acute tubular necrosis is that of Hall, Johnson, Maher and Hunt.[28] These authors followed 36 patients three to 126 months after initial recovery from acute renal failure due to multiple causes. Fourteen (39%) regained normal renal function. Their mean age was 32 years and mean duration of oliguria 10.2 days. The 22 (61%) whose renal function failed to return to the expected normal for their age had a mean age of 49 years and mean duration of oliguria of 16 days. Patients

*Travenol Laboratories, Inc., Morton Grove, Illinois.

under age 50 attained maximum recovery by six months whereas older patients required as long as one year. On an average, patients over age 40 regained no more than 75% of the normal renal function expected for their age. The presence of prior renal disease did not appear to affect the degree of recovery.

Somewhat disturbing was the finding by the same authors that in seven of nine patients followed greater than seven years the inulin clearance declined an average of 17.6% from the maximum attained. The reason for this late deterioration is not known. Renal biopsies were not obtained.

Lewers[33] found that only 33% of 30 patients followed two to 15 years after acute tubular necrosis (mean 9.3 years) eventually attained both a normal creatinine clearance and concentrating ability. A progressive late decrease in creatinine clearance occurred in two of eight patients followed by serial studies for four or more years after the initial recovery.

Although a general review of the literature fails to demonstrate a definite correlation between the severity of the illness causing the acute renal failure and the ultimate functional recovery, the clinical data of Hall et al.[28] and the histologic studies of Muehrcke et al.[31] do suggest that the longer the period of oliguria the greater the final histologic abnormality and the greater the degree of ultimate renal functional impairment.

It must be remembered that despite inability to attain complete recovery of renal function and possible late deterioration, all patients with acute tubular necrosis due to ischemic injury who survive their primary disease and pass through the diuretic phase of their renal failure achieve enough function to avoid long-term dialysis. A creatinine clearance of 10 ml/min/1.73 m^2 in conjunction with good conservative medical management is all that is necessary.

The 80% survival for the five cases presented in this report probably can be attributed to a combination of factors—intensive medical care, frequent dialysis, young age, a small series and fortuity.

Conclusion

With good conservative therapy and appropriate application of dialytic principles the physician can offer the younger patient with acute tubular necrosis due to "medical causes" a relatively good prognosis. A more grim prognosis awaits the patient with acute renal failure secondary to surgical or traumatic causes, especially if he is elderly (over age 60). The return of renal function in those that survive the period of acute failure usually is excellent even though 12 months may be required to attain maximum function. The recent evidence of deteriorating renal function years later is somewhat disquieting, however. It may be that some cases that are classified as acute tubular necrosis but subsequently show a poor return of renal function actually are examples of patchy cortical necrosis or other renal pathology.

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21-33. Will be found on page 42.

The Nephrotic Syndrome

A New Look at the Pathology and Pathophysiology

BARBARA A. BURKE, M.D.,* S. MICHAEL MAUER, M.D.,* ALFRED J. FISH, M.D.,*
ALFRED F. MICHAEL, M.D.,* AND ROBERT L. VERNIER, M.D.*

The purpose of this paper is to briefly review the principal morphologic and immunologic characteristics of the glomerular lesions found in patients with the nephrotic syndrome and to comment on the value of such studies in the management of this disorder. The recent advances in understanding the pathophysiology of the syndrome are also reviewed.

THE PURPOSE OF THIS paper is to review the principal morphologic and immunologic characteristics of the glomerular lesions found in patients with nephrotic syndrome and to comment on the value of such studies in managing this disorder. Recent advances in understanding the pathophysiology of the syndrome will also be reviewed.

Use of percutaneous kidney biopsy techniques the past 15 years has improved our understanding of the pathology of the nephrotic syndrome. Fluorescence microscopy has also clarified immune mechanisms and electron microscopy has helped us understand it even farther.

In the Table we summarize the morphology of the nephrotic syndrome, as developed for a large series.[1] The Table emphasizes the pathologic lesions that may be recognized in renal biopsy specimens. The Table also emphasizes the correlation between renal pathology and response to adreno-cortical steroids in the various forms of this disease.

*Departments of Pathology and Pediatrics, University of Minnesota, Minneapolis, Minnesota.

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Minimal Lesion

As shown in the Table, the minimal lesion (nil lesion) occurs mostly of children, and less frequently in adults. Still it represents 20-30 percent of patients in several larger adult series. Recognizing this lesion is important since most patients lesion) occurs mostly in children, and less frewith this lesion will have a complete remission with adrenocortical steroid therapy.

On light microscopy, biopsy specimens from such patients show no obvious abnormality. There may be minimal or equivocal increase in mesangial matrix and/or minimal or equivocal mesangial hypercellularity. The descriptive terms "sclerosis" and "proliferation" are not applicable to these specimens[2]. Immunofluorescence microscopy reveals either no deposits of immunoglobulins in glomeruli or the presence of stalk (mes-

TABLE
Principal Morphologic Lesions of Nephrotic Syndrome and Response to Optimal Steroid Therapy (*)

	% Incidence		% Response	
	Children	Adults	Children	Adults
Minimal Lesion (Idiopathic)	70-80	20-30	75-90	50-75
Focal Sclerosis	7-10	?	0	?
Membranous Nephropathy	1-5	10-25	0	0
Proliferative Glomerulonephritis (GN (includes membranoproliferative GN)	10-15	30-40	5-10	0-5
Nephrotic Syndrome in: amyloid, lupus erythematosus, anaphylactoid purpura, diabetes mellitus, etc.	5-10	20-25	0-5	0.5

*Modified from ref #1.
? = data not available.

angial) deposits. These deposits consist principally of IgM and/or B_1C globulins. The globulins may be a consequence rather than a cause of proteinuria.[3,4]

Serum levels of complement are generally within normal limits. Some patients have a decrease in the level of C_3 PA, a C_3 proactivator.[4] Urinary loss of this BETA globulin with relatively low molecular weight (80,000) may account for the low serum levels of C_3 PA in these patients (unproven).[4]

There is thus no conclusive proof that this form of nephrotic syndrome is immunologically mediated. Electron microscopy of this lesion shows a more or less diffuse fusion of foot processes (Figure 1). These findings are more prominent with massive proteinuria and less evident in patients in remission.[5] Patients with this lesion generally have a highly selective proteinuria, no hematuria or transient presence of RBC in the urine, onset after the first year of life, and a good response with remission of the disease with adequate adrenocorticosteroid administration.[2,5-9]

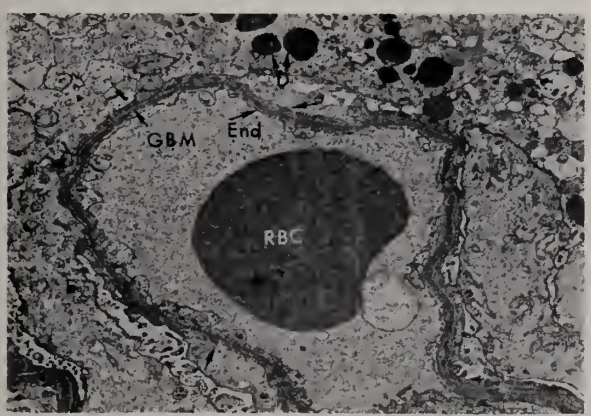


Fig. 1—Electron micrography of a typical capillary loop from a patient with minimal lesion nephrotic syndrome. Note the diffuse loss of epithelial cell (E) foot processes (arrows) over the entire surface of the glomerular basement membrane (GBM). The GBM is normal in thickness and density, the endothelium (End) is thin and normal. Numerous dense droplets (D) representing protein-lipid reabsorption are seen in one epithelial cell. The lumen contains precipitated protein and a red blood cell (RBC). Magnification 10,000 X.

Focal Sclerosis

About 7-10% of children with apparent minimal lesion develop a focal lesion. This first appears in the corticomedullary nephrons and is termed focal sclerosis. Habib and Kleinknecht[6] first focused attention on the prognostic implications of this lesion, although Rich first described it.[10] Patients with this lesion have both focal and segmental glomerulosclerosis. At first the sclerosis may involve only a portion of one lobule of only a few glomeruli, the remaining glomeruli showing no conspicuous change i.e. histopathologic findings identical with those in the minimal lesion group of patients. The sclerosed foci reveal hyaline material in mesangium and obliterated capillary walls and lumena (Figure 2). Mesangial cellularity may be normal, increased, or decreased. Often the sclerosed lobule adheres locally to the capsule where there is often a small crescent present.

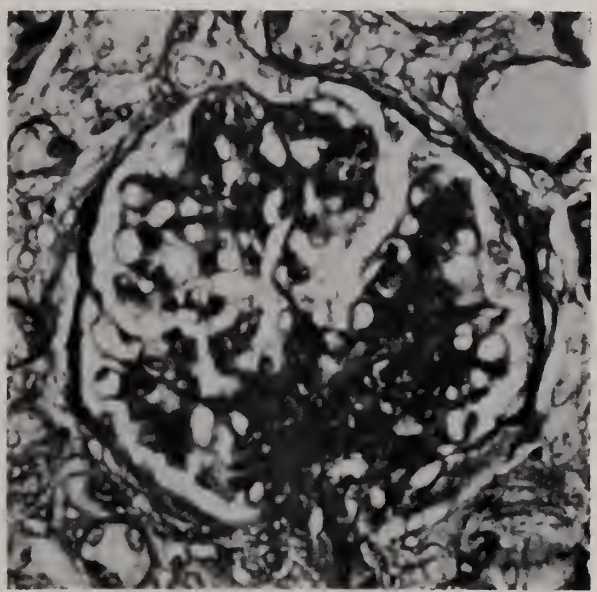


Fig. 2—Light micrograph of a typical glomerulus showing a large focal area of sclerosis in a biopsy from an 18-year-old boy with steroid resistant nephrotic syndrome of 10 years duration. Note the adhesion of the lobule to Bowman's capsule (PAS stain, magnification 400 X).

Relationship

The relationship between minimal lesion nephrotic syndrome and focal sclerosis is as yet unknown though the finding of early focal sclerosis on initial biopsy in some patients, however, has led some investigators to speculate that the lesion does not develop from the minimal (nil) lesion but is present from the onset.

Because these lesions predominate in the nephrons at the corticomedullary junction[10], because they are focally distributed, and because only a few nephrons are involved initially, they will be missed if the biopsy specimen is small and does not contain corticomedullary nephrons. An erroneous impression that the patient has a minimal lesion will be gained. Identifying patients early with focal, segmental, glomerulosclerosis is important because these patients are usually steroid resistant and many have progressive disease leading to chronic glomerulonephritis.[2,6,7,10-14] Serial sectioning of initial biopsy specimens from nephrotic patients with apparent minimal (nil) le-

sions may reveal unsuspected focal segmental glomerulosclerosis, thereby providing important therapeutic and prognostic information.[15]

Immunopathologic studies reveal little difference between the two groups of patients with the exception that glomeruli showing segmental sclerosis often contain deposits of immunoglobulins, especially IgM and B_1C, in the sclerotic focus.[4]

Steroid Responsiveness

Adrenocorticosteroid responsiveness of one group and virtual steroid resistance of the other has led some to suggest there are important biochemical differences between these two lesions.[4] Furthermore, when patients with focal sclerosis progress to chronic glomerulonephritis and undergo homotransplantation, nephrotic syndrome may recur with focal sclerosis in the transplanted kidney. This has been documented in many cases (four out of six at the University of Minnesota Hospitals). This suggests that the pathogenesis of the disease in such patients involves systemic circulating factors.[16,17] Patients with focal sclerosis are usually initially steroid resistant, have persistent hematuria, and either poorly selective or nonselective proteinuria.[2,6]

Global Sclerosis

In a few instances in Habib's and Kleinknecht's cases, the focal lesion was global rather than segmental so that normal and completely hyalinized glomeruli were found together with no intermediary stages[6]. Tubular and interstitial changes were thought to be in proportion to the intensity of the glomerular changes in these cases. This group of patients had the same clinical features and prognosis as the focal, segmental sclerosis patients with the exception that renal failure occurred earlier in the patients with segmental sclerosis (average four years five months) than in those with global sclerosis (average seven years)[6].

Care in interpreting the significance of an occasional hyalinized glomerulus is essential. Hyalinized glomeruli can be found postmortem at any age in patients dying accidentally without previous clinical evidence of renal disease, and their interpretation must be made in the context of the clinical data. The same precautions are necessary when a single glomerular showing segmental sclerosis is encountered in an otherwise normal biopsy specimen.

Arteriolar Hyaline

Subendothelial arteriolar hyalinization was found in 25% of Habib's and Kleinknecht's cases of focal sclerosis and has been described by others[6,7,13]. No prognostic significance was found for these lesions by Jao et al. in their patients.[7]

Mesangial Proliferative Lesion

A mesangial proliferative lesion resembling that found in patients with poststreptococcal glomerulonephritis occurs rarely in patients with nephrotic syndrome. In these patients, glomeruli show slight but diffuse mesangial cell hyperplasia accompanied by a moderate increase in mesangial matrix material which is both Schiff and silver positive (Figure 3). Capillary wall thickness and lumen size are normal. All patients with this lesion behaved like those with the nil lesion in the report of the International Study of Kidney Disease in Children published by Churg et al. (4 cases out of 127)[2], while all of the patients reported by Jao et al. with this lesion had persistent proteinuria after corticosteroid therapy (three cases out of 42)[7]. Further evaluation of the therapeutic and prognostic implications of this lesion are needed before final conclusions may be drawn.

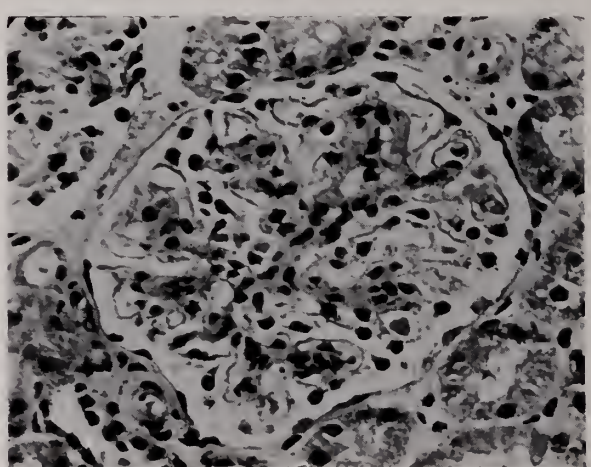


Fig. 3—Glomerulus showing mesangial proliferative lesion. Hematoxylin-eosin stain. Magnification 400 X.

Membranous Glomerulonephritis

Membranous glomerulonephritis (extramembranous nephropathy), commonly associated with nephrotic syndrome in adults, is nevertheless encountered in pediatric patients. In this condition, there is diffuse, homogenous thickening of the glomerular capillary wall due to deposited immunoglobulins and complement in a subepithelial position on the glomerular basement membrane (GBM) (Figure 4). Minimal mesangial cell proliferation may be present. Silver stains reveal sil-

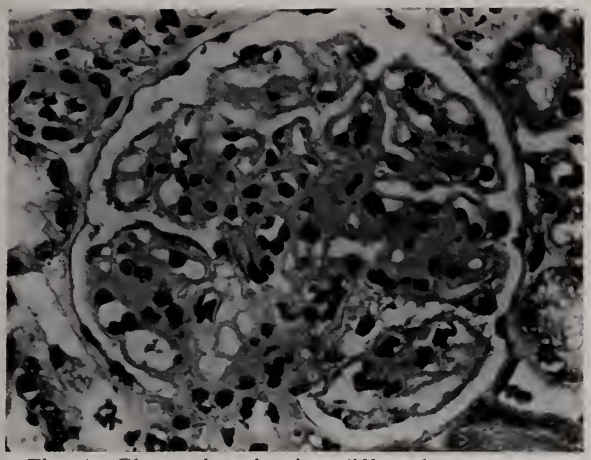


Fig. 4—Glomerulus showing diffuse basement membrane thickening (membranous glomerulonephritis). Hematoxylin-eosin stain. Magnification 400 X.

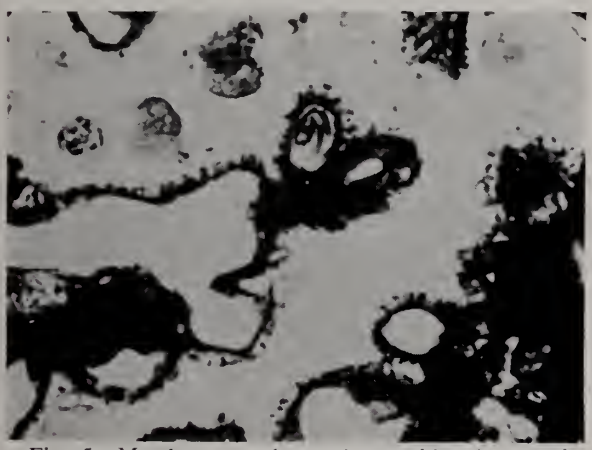


Fig. 5—Membranous glomerulonephritis, silver stain, showing "spike" projections of GBM extending from the true GBM. Glomerulus. Magnification 1000 X.

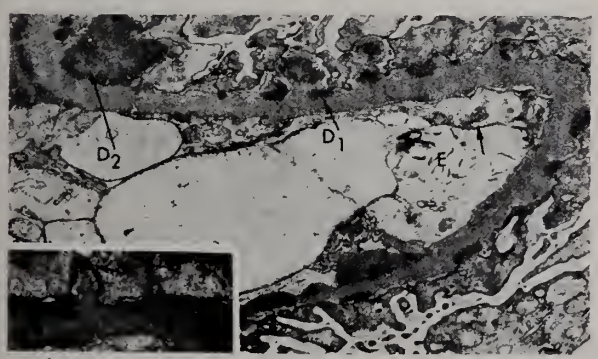


Fig. 6—Electron micrograph of a capillary loop in a biopsy specimen from a patient with early membranous glomerulonephritis and systemic lupus erythematosus. The capillary lumen is filled with swollen endothelial cell blebs (E) and several small clusters of tubular "viral-like" particles (arrow) are seen within the endothelium. Dense deposits of variable size are seen within the basement membrane (D_1) and beneath the epithelium (D_2). The insert shows a basement membrane spike (S), an extrusion of GBM material into the epithelial slit between two deposits; a more advanced lesion of membranous nephritis. Magnification 18,900 X. Magnification of insert 25,000 X.

ver staining of the endothelial side of the GBM which represents the true GBM. Many silver positive spikes extend from it perpendicularly toward the epithelial side. Between these spikes are areas that do not take the silver stain but stain red with Masson trichrome and azocarmine stains (Figure 5). Electron microscopy reveals subepithelial electron dense deposits between which there are projections from the GBM correlating with the silver positive spikes seen by light microscopy (Figure 6)[18-21] In later stages, the GBM projections may extend upward to cover the deposits. In these cases, the GBM may have a split appearance on silver staining with the two parallel laminae connected by cross bars of GBM (the so called Railroad Track appearance together with railroad ties). In some instances, the dense deposits disappear.

Immunofluorescence demonstrates a diffuse granular deposition of IgG and B_1C globulin which follows the distribution of the GBM (Figure 7). This pattern correlates with the electron dense bodies seen by electron microscopy and the non argyrophilic (but red staining with Masson trichrome and azocarmine stains) portion of the GBM seen by light microscopy[19]. Membranous glomerulonephritis is one of the many forms of glomerulonephritis which are thought to be mediated via circulating antigen-antibody complexes which lodge in the glomerular



Fig. 7—Fluorescent micrograph of several capillaries from a glomerulus of a patient with membranous glomerulonephritis. The beaded appearance of the capillary walls result from the specific localization of fluoroscein labelled ant-human IgG in deposited antibody complexes. Magnification 1400 X.

capillary basement membrane where they cause injury.

Role of Immunofluorescence

The above descriptions of membranous glomerulonephritis pertain to the mild to moderately advanced case. In the initial phase of this disease, hematoxylin-cosin stained sections show at most only a questionable thickening of the glomerular capillary wall and silver and Masson trichrome stains may show only equivocal findings. It is in this early stage that immunofluorescence microscopy is an invaluable aide in differentiating membranous nephritis from the nil lesion nephrotic syndrome. The distinction is therapeutically important since corticosteroids and other immunosuppressive drugs are currently considered ineffective therapy for patients with membranous nephritis. Even in early membranous nephritis, fluorescence microscopy reveals diffuse fine granular membrane oriented deposits of IgG and B_1C globulin.

Membranous Glomerulonephritis in Children

The nephrotic syndrome is frequently not intense in children with membranous glomerulonephritis and the disease seems to have generally a more benign course in children than adults[22,23]. A severe and persistent nephrotic syndrome and persistent hematuria seem to indicate a poor prognosis[6].

Of particular interest is the association between membranous glomerulonephritis in children and systemic lupus erythematosus (SLE). At the University of Minnesota Hospitals, we have studied 10 children with membranous glomerulonephritis of whom six either were found to have SLE when the membranous lesion was discovered (three cases) or who developed SLE one 5/12 to three 8/12 years later (three cases)[24]. Four of these patients had a nephrotic syndrome. In five of the six SLE cases, the diagnosis of SLE was predicted because of the localization of IgA (±IgM) antibody in a granular deposition along the GBM on immunofluorescence together with the expected IgG and B_1C globulin. All six SLE cases had microtubular structures in glomerular endothelial cells by electron microscopy. The children with membranous nephritis without evidence of SLE had neither IgA antibody on immunofluorescence nor microtubular structures by electron microscopy. Thus the finding of membranous nephritis should alert the physician to initiate an intensive investigation for systemic lupus erythematosus.

Membranoproliferative Glomerulonephritis

Membranoproliferative glomerulonephritis (MPGN) is characterized histologically by proliferating mesangial cells, and increased mesangial matrix, and diffuse irregular thickening of the capillary walls due to interposition of mesangial cell cytoplasm and basement membrane-like material between the true basement membrane and the endothelium.[6,25,26] As a consequence, there is

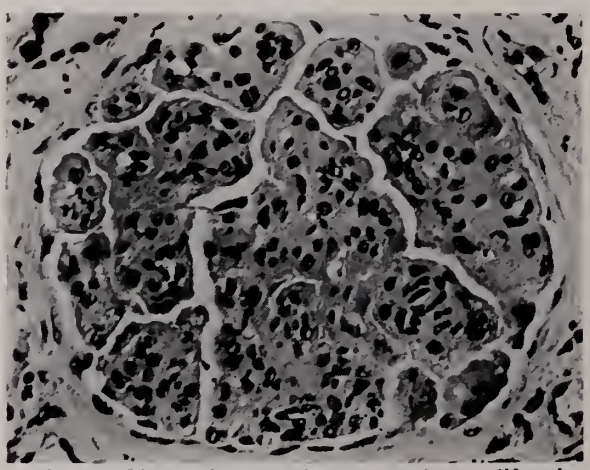


Fig. 8—Glomerulus showing mesangial proliferation and sclerosis plus diffuse capillary wall thickening (membranoproliferative glomerulonephritis. Hematoxylin-eosin stain. Magnification 400 X.

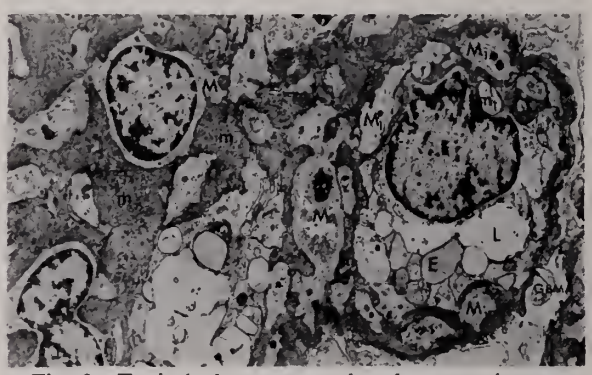


Fig. 9—Typical changes seen by electron microscopy in advanced membranoproliferative glomerulonephritis. The mesangial matrix (m) on the left is greatly increased and consists of broad interconnected bands separated by segments of mesangial cell cytoplasm (M). Note that cell processes of the mesangium (M_1) also extend partially around the capillary to the right as cross sectioned processes, which lie between the true basement membrane (GBM) which is irregular in thickness and contains some dense deposits, and the swollen endothelium (E). Trabeculae of mesangial matrix (m-1) form a discontinuous "new" membrane which accounts for the "splitting" of the GBM seen with silver impregnation methods in similar specimens. Magnification 7000 X.

progressive narrowing of the capillary lumen and with well advanced lesions, the glomerular tufts have a lobulated appearance (Figure 8). By electron microscopy, many mesangial cell cytoplasmic processes can be seen between the GBM proper and the cytoplasm of endothelial cells lining the capillary lumen (Figure 9). In many instances, a fine strand of basement membrane-like material parallel to the true GBM, separates the mesangial cell cytoplasm from the endothelium and accounts for the double contour or split basement membrane effect seen in silver and PAS stains (Figure 10). Non-argyrophilic dense deposits may be found beneath the GBM proper.[20,26] Immuno-pathologic studies typically reveal a characteristic peripheral lobular deposition of B_1C globulin (C_3) and properdin on the GBM in severely affected glomeruli (Figure 11). IgG and/or IgM globulin are present in the glomeruli in approximately ⅔ of the patients and C_{1q} and C_4 are often present[26].

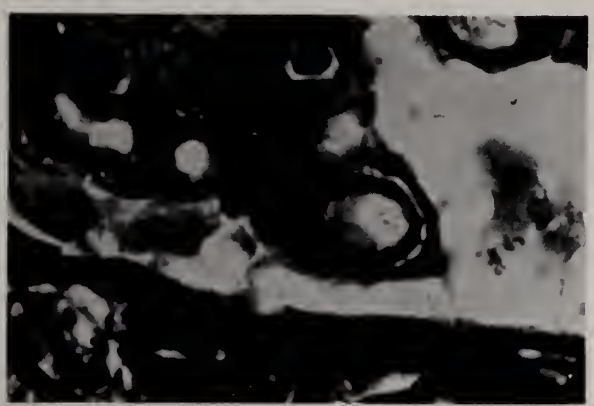


Fig. 10—Membranoproliferative glomerulonephritis. Silver stain, showing "splitting" of the GBM typical of this disease. Glomerulus. Magnification 1000 X.

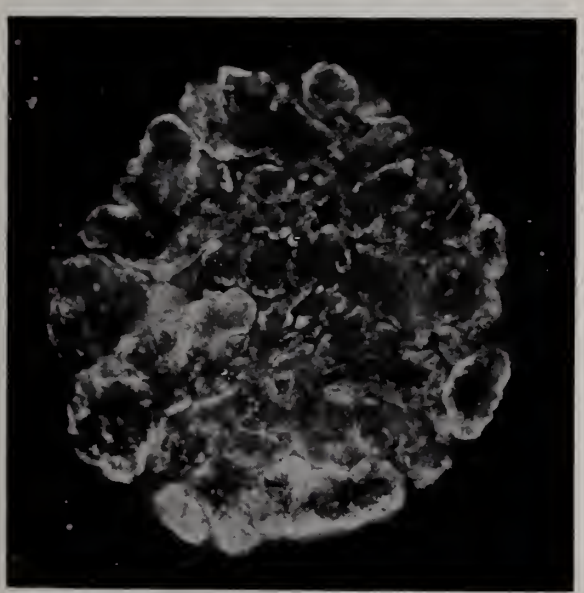


Fig. 11—Fluorescent micrograph of the typical peripheral-lobular pattern of deposition of B-1-C globulin on a glomerulus from a patient with membranoproliferative glomerulonephritis. Note the fluorescent positive granules at the periphery of the lobules (best seen on the left), with relatively negative central regions which represent the expanded mesangium. Magnification 400 X.

Complement Levels

Characteristically, serum levels of total hemolytic complement and C_3 are depressed while those of C_2 are normal and those of C_1 and C_4 are often though not always normal[26]. Hypocomplementemia is probably not a necessary feature of the syndrome in patients who have characteristic renal morphology since there is considerable variation in the levels of C_3. Periods of normocomplementemia may alternate with periods of hypocomplementemia and serum complement levels may increase following therapy with prednisone, immunosuppressive drugs, and heparin and following nephrectomy and renal transplantation.

Complement Activation

Two distinct mechanisms of complement activation have been suggested as potential mediators of glomerular injury[26,27]. The classical mechanism of activation is thought to involve immune complexes since IgG and IgM globulins as well as early complement components (C_{1q}, C_2, C_4, and C_3) are frequently found on the glomerular capillary in diseases such as SLE. In membranoproliferative glomerulonephritis, an alternate pathway of complement activation may be operating. The alternate mechanism is suggested because of the marked decrease in serum level of C_3 with relatively normal levels of earlier components (C_1, C_4, C_2). Furthermore, the presence of a serum complement inhibitor that inactivates C_3 preferentially, the identification of a serum lytic system that cleaves B_1C and the demonstration in glomerular deposits of properdin, a protein which is known to be associated with the alternate pathway of complement activation, all lend credence to this suggestion. The absence of detectable antibody globulins in the glomeruli of some patients is further evidence in favor of an alternate mechanism. Perhaps both mechanisms play a role.

Nature of Nephrotic Syndrome

Approximately one-third of the patients with membranoproliferative glomerulonephritis present with a nephrotic syndrome and all are steroid

resistant.[6,26] An intense, relentless, nephrotic syndrome, persistent hematuria, and early onset of renal failure are correlated with a poor prognosis[6]. Renal insufficiency develops in virtually all patients, although the rate of progress of the disease varies greatly and some patients survive for many years.

Lobular glomerulonephritis, whieh some investigators distinguish from MPGN by the presence of centrolobular nodules of mesangial matrix material, has the same clinical features, immunofluorescence, and outeome as MPGN except that survival is said to be longer[6]. Others do not reeognize this subentity.

Dense Deposit Disease

Dense deposit disease (also ealled membranoproliferative glomerulonephritis with dense deposits) is a rare morphologic lesion characterized by the presenee of an abnormal dense substance in the basement membranes of the kidney i.e. those of the peripheral glomerular capillary, Bowman's capsule, the renal tubules, and peritubular capillaries[28]. An identieal deposit may be found in the mesangium. The substance is strongly eosinophilic and PAS positive but is silver and carmine negative (Figure 12). By electron mieroscopy, the substance is dense and without definite structure and is located in mesangium and eentrally within the lamina densa of the basement membranes. A mesangial proliferative glomerulonephritis with or without crescents is also found. Immunofluorescence in well established cases shows complement eomponents in the deposits and some patients have decreased serum complement levels. A recent report of three cases of this disease implicates a relationship between dense deposit disease and streptocoeeal disease including non-group A streptococei[29]. The authors of this report conclude, however, that this uncommon renal lesion is probably a nonspeeific reaction to a variety of stimuli.

Clinically, most of these patients are young adults though the disease occurs in children, often presenting as an aeute glomerulonephritis with hematuria and proteinuria. Approximately 12% have onset as the nephrotic syndrome but two-thirds are said to develop a nephrotie syndrome during the course of the disease which is steroid resistant.[28] The course is variable, some having stable disease, some progressive renal insufficiency, and some reeurrent episodes of reversible renal failure. The appearance of the nephrotic syndrome and amierobial leukocyturia is said to be ominous. Reeurrence of the identical disease after transplantation suggests a systemic abnormality[28].

The nephrotic syndrome occurring under the age of one year has a uniformly poor prognosis

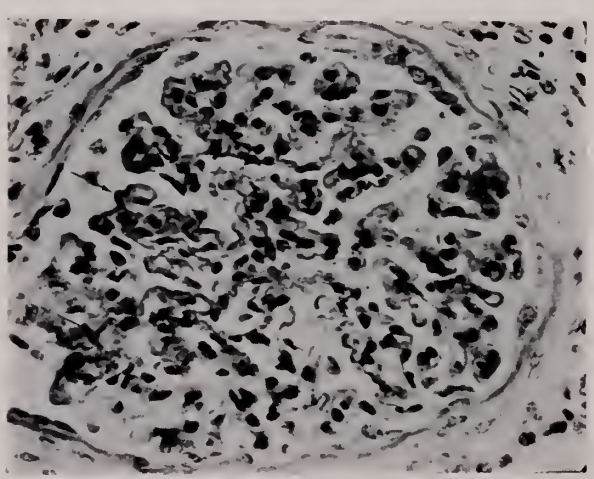


Fig. 12—Dense deposit disease, PAS stain, showing PAS positive dense deposits within the GBM (arrows). Note also the dense deposits within Bowman's capsular basement membrane Glomerulus. Magnification 400 X.

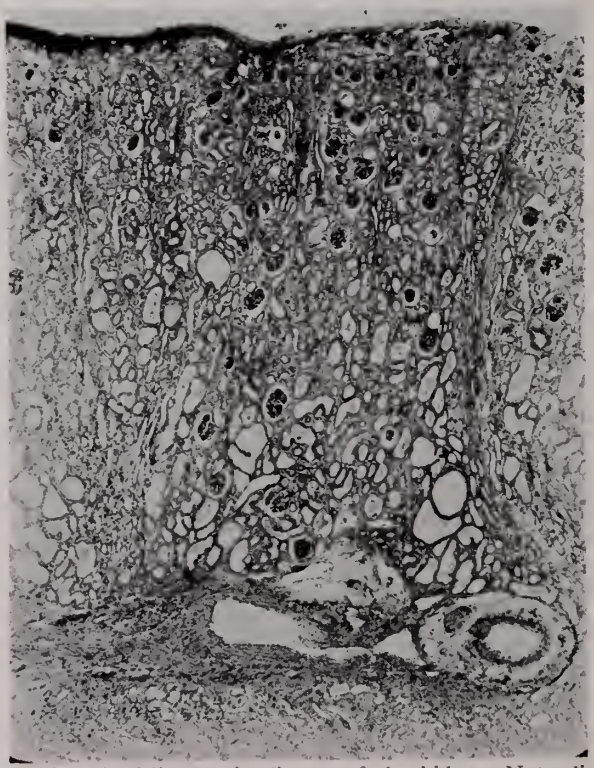


Fig. 13—Microcystic disease of the kidney. Note dilated proximal convoluted tubules particularly those in the deep cortex together with dilated Bowman's capsules. Hematoxylin-eosin stain. Magnification 25 X.

unless it has a known cause such as congenital syphilis or mercury induced nephrosis.[30-34]

Microcystic Nephrotic Syndrome

Microcystic nephrotic syndrome, an hereditary, autosomal recessively transmitted defect presents in infancy, usually by four months of age in children of Finnish ancestry.[35] The kidneys from such patients are grossly normal but microscopically one finds cystic dilatation of Bowman's capsule and dilatation of some proximal convoluted tubules. These changes may be localized to the deep cortex in some patients and is of irregular distribution in others (Figure 13).[36,37,38] The appearance of the dilated tubules is that of compensatory hypertrophy. Oliver, who named the condition, described areas of atresia and disruption of tubules in microdissection studies.[37]

Infants with this lesion are all steroid resistant and all develop chronic glomerulonephritis. If they can be kept alive until they reach suitable age for transplantation, they can be successfully transplanted and do not develop their original disease again in the transplanted kidney[39]

Immunofluorescent studies of the University of Minnesota cases revealed no immune deposits in most. Focal and segmental IgG, IgM, and B_1C deposits were found only late in the course of the disease of only one patient probably related to the duration of the disease and not to specific localization[38]. This disease is a relatively rare cause of nephrotic syndrome even in a state with a relatively large population of Finnish ancestry.

There are other causes of the nephrotic syndrome in children, some of the familial variety with special features but these entities are beyond the scope of this paper.

Pathophysiology of Proteinuria

The major early functional defect in the nephrotic syndrome is an increased permeability of the glomerular capillary wall to serum proteins. Most data supporting this hypothesis comes from studies of experimental models of the nephrotic syndrome produced in laboratory animals. The drug aminonucleoside of puromycin (AN) will regularly induce a nephrotic state in rats, which resembles in many ways the minimal lesion nephrotic syndrome of man[40]. Oken et al.[41] have recently confirmed that the glomerular filtrate of the rat normally contains very little protein and that the protein concentration in the glomerular filtrate of rats with AN nephrosis is increased 10-40 fold. Hoyer et al.[42] have demonstrated by a series of renal transplantation and perfusion experiments that AN affects the kidney cells directly but the precise cell involved and the mechanism of induction of increased glomerular permeability remains unknown.

Glomerular Capillary Wall

The glomerular capillary wall has a unique and complex morphology which has been partially resolved with the aid of recent histochemical, biochemical, electron microscopic, and scanning electron microscopic techniques. The morphologic components which would act as barriers to passage of macro molecules or filter components include the endothelium, the basement membrane and the epithelium, including the filtration slits and the filtration slit membrane (Figures 14-15).

The endothelium consists of attenuated cells about 400 Å thick over most of the peripheral loop and containing numerous holes or fenestrae. The fenestrae measure about 400-1000 Å* in width and some are covered by a very thin membrane.

Basement Membrane

The basement membrane (GBM) appears with suitable staining to consist of three layers: the lamina rara interna, the central lamina densa, and the lamina rara externa (Figures 14-15). With favorable thin sections, a fine fibrillar network is visible within the more electron dense central zone with fine fibrils extending perpendicularly from the lamina densa into the lamina rara. The total GBM width varies among species and with age but is about 2600 Å units in width in the adult man.[43]

Biochemical studies indicate that the GBM is composed of an unusual collagen-like protein which contains hydroxyproline, increased hydroxylysine, and twenty times as much hexose as tenden collagen. The principal carbohydrate in this unusual glycoprotein is a glycosyl-galactose with significant amounts of mannose, fucose, hexosamine and sialic acid (see Kefalides[44] for review). Thus in life the GBM probably consists of a collagen-like fibrillar network enmeshed in a heteropolysaccharide gel.

*Å = Angstrom unit. 1 micron = 10,000 Å.

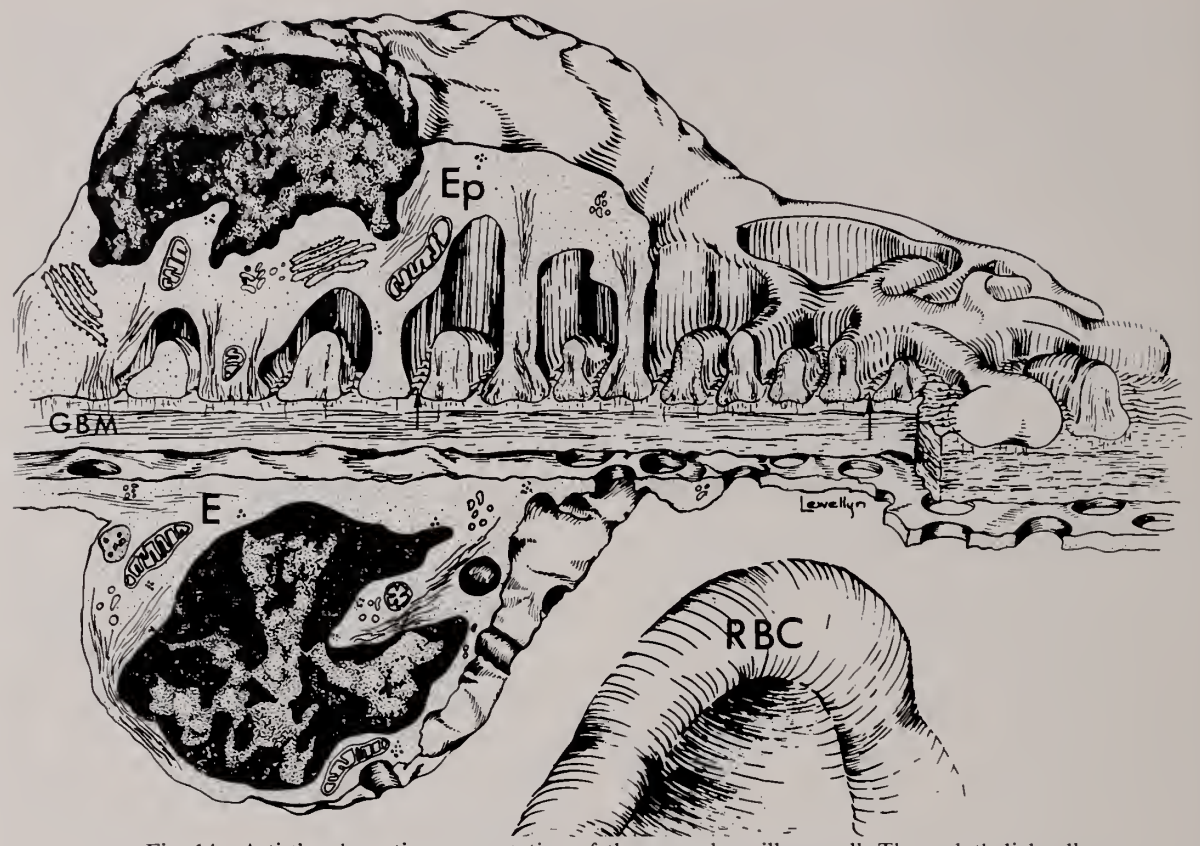


Fig. 14—Artist's schematic representation of the normal capillary wall. The endothelial cells (E) form a thin perforated layer around most of the capillary loop and the ± 1000 Ångstrom pores are illustrated on the right. The basement membrane (GBM) fills the space between the endothelial cells and the limiting membrane of the epithelial cells (Ep) at the level of the foot processes. The fine fibrillar characteristic of the GBM is suggested. Note that the filtration slits between the foot processes (arrows) are bridged by a delicate filtration slit membrane. The complex organization of epithelial cell processes and foot processes is shown. Artist: Ms. Jeanette Lewellyn, technical artist in Dr. Vernier's laboratory.

Podocytes

The glomerular epithelial cells have also been called podocytes because of the complex system of primary and secondary cytoplasmic processes which they extend to the GBM ending with the foot processes. The foot processes appear to be embedded within the lamina rara externa of the GBM, and are separated from one another by relatively narrow spaces (200-300 Å), the epithelial slits. A delicate membrane, the epithelial slit membrane, extends between the adjacent epithelial foot processes near and parallel to the GBM. The filtration slit is continuous with the urinary space. The epithelial slits widen beyond the slit membrane, but the shape is variable, de-

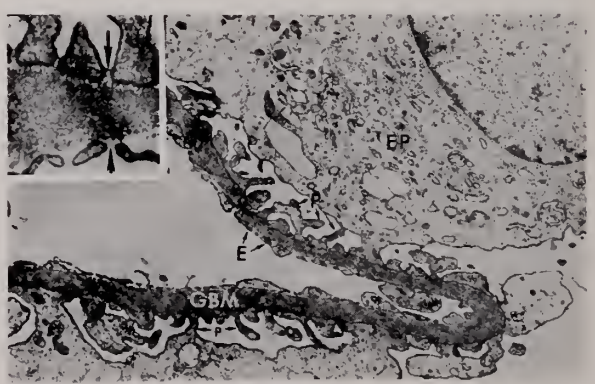


Fig. 15—Electron micrograph of a glomerular capillary loop of a normal human kidney. The structures illustrated in Figure 14 are shown. The insert shows at higher magnification details of the filtration slit and membrane (arrow) and the endothelial pores (bottom arrow). Ep = epithelium, E = endothelium, GBM = glomerular basement membrane, p = epithelial foot processes. Magnification 12,800 X. Insert 43,000 X.

pending upon the conditions of fixation and the shrinkage which occurs in preparation and in life, the spaces are probably uniformly narrow slits.

Histochemical studies demonstrate that the entire epithelial cell surface and the surfaces of the foot processes (thus the filtration slits) are coated with an unusual glycocalyx which contains acid mucopolysaccharides and sialic acid, which are readily demonstrated with stains such as colloidal iron and alcian blue[45]. Under appropriate conditions of pH, the slime of glycoprotein coating these cells is the only material stainable within the cortex, emphasizing the probable unique functional importance of this material, of which more will be said later.

Functional Structures

The probable function of some of these unique morphologic structures which form the capillary wall have been revealed by recent ultrastructural tracer studies. The methods involve intravenous administration to normal animals of electron dense particles of variable sizes, or the use of enzymes, notably peroxidases of graded sizes. Early studies utilized relatively large particles such as ferritin (diameter 60 Å, molecular wt 460,000). Such particles were shown to readily penetrate the endothelium and after injection were found primarily within the lamina rara of the GBM, indicating that this layer of the capillary wall was an effective filter and barrier for large molecular weight proteins[46]. The enzyme tracer methods utilize the peroxidase reaction with 3,3′-diaminobenzidine (DAB) as an electron donor, and in the presence of hydrogen peroxide, DAB is oxidized to an insoluble polymer. This reaction product has a high affinity for osmic acid with which the treated tissue is stained, to give an electron dense image in the electron microscope at the site of the peroxidase enzyme.

In the series of remarkable studies, Karnofsky et all.[47] have shown that small enzymes such as cytochrome c (diameter 15 Å, mol. wt. 12,000) readily penetrate all layers of the capillary wall and pass through the filtration slits and into the urinary space without apparent restriction. Horseradish peroxidase (30 Å; mol, wt. 40,000) was noted to be retarded somewhat by the GBM but to pass through the filtration slits into the urinary space. Larger enzymes such as myeloperoxidase (44 Å; mol. wt. 160,000-180,000) were retarded but slowly passed through the GBM, to the level of the filtration slit membrane in small quantities at early time period. At later times, the larger molecules appeared to collect under the filtration slit membrane, and very small quantities reached the filtration slits and the urinary space. Karnovsky concluded that the filtration process for proteins is graded and involves two structures of the capillary wall, the GBM and the filtration slits and filtration slit membrane. The former restricts the passage of proteins over a large range of molecular weights but is most effective for larger molecules. The epithelial slit represents the final filter for relatively smaller molecules and probably effectively excludes molecules larger than albumin (mol. wt. 40,000) from passage to the urinary space.

If in life the epithelial cell filtration slit is a long (3000-5000 Å), uniformly narrow space filled with a glycoprotein, current evidence suggests this structure is the critical barrier which is altered in disease states associated with albuminuria.

Electron microscopic studies of the glomerular capillary wall in the nephrotic syndrome of diverse etiologies, have demonstrated a consistent alteration of the epithelium, and in the nil lesion nephrotic syndrome, this abnormality may be the only recognized ultrastructural pathology[5]. The abnormality consists of a loss of foot processes over much of the capillary surfaces, which are covered instead by a continuous layer of epithelial cytoplasm (Figure 1). This abnormality has been shown to develop with the appearance of proteinuria in the AN nephrotic rat[40] and to be reversible in children with the nil lesion nephrotic syndrome, in whom sequential renal biopsy specimens have demonstrated return of foot processes to normal form with cessation of proteinuria[49].

Yet the relationship of this striking change in morphology to the cause of proteinuria is not clear, since other studies in animals have shown that partial foot process loss occurs with "threshold" proteinuria. Animals given intravenous albumin in quantities sufficient to raise the serum albumin to very high levels develop proteinuria and on biopsy demonstrate a partial loss of foot processes, which is promptly reversible with cessation of the infusion[48,50]. These studies suggest that loss of epithelial foot processes may be a response to protein reaching the filtration slit, rather than a cause of proteinuria.

Glycoprotein of Epithelial Cells

Studies of the glycoprotein which coats the epithelial cells of the glomerulus, and fills the filtration slits as indicated earlier, may provide important clues to the mechanism of proteinuria. The concentration of this material is markedly decreased in the nephrotic syndrome of both experimental animals [45,51] and man [52]. Since this glycoprotein may restrict protein transport through charge and ionic effects, and since decreased concentrations have been demonstrated in glomeruli during proteinuria, possibly loss of this material is a primary event in the mechanism of proteinuria. Also loss of this material may be related directly to the fusion of epithelial cell foot processes (Figure 1). The association of proteinuria with the membranous nephropathy might perimental animals[45,51] and man.[52] Since this glycoprotein may restrict protein transport through charge and ionic effects, and since also relate to an abnormality of the synthesis or the loss by other mechanisms of this glycoprotein as a conseqence of the deposition of immune complexes of a specific size or charge in the region of the epithelial cell membrane and foot processes (Figure 6). Additional studies of this type will lead to either support for or rejection of this interesting hypothesis. Additional research will be necessary to provide a rational scientific base for the development of effective treatment for poorly understood nephrotic syndromes.

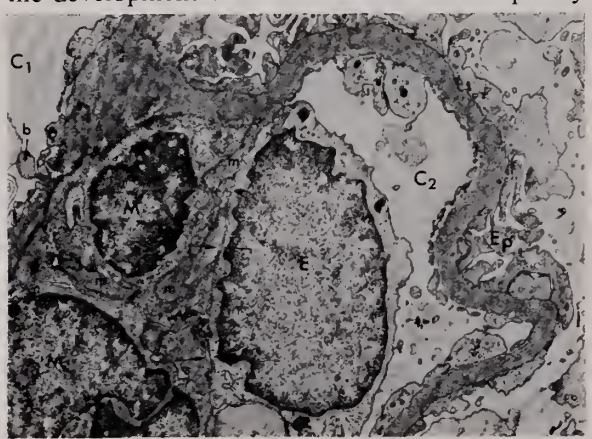


Fig. 16—Portion of a mesangial region and two capillaries from a lobule of a glomerulus from a normal kidney donor. The center left shows two mesangial cells (M) and narrow strands of matrix (m) between the cells. These mesangial matrix regions are part of the potential mesangial channel system described in the text, and some appear as narow spaces in this specimen (arrow). The interface of capillary #1 (C-1) shows a thin endothelium covering the mesangium and a small mesangial process (bleb) (b) protruding into the lumen between endothelial segments. In capillary #2 (C-2) an endothelial cell (E) and its nucleus cover the interface with the mesangium. EP = epithelium. Magnification 15,500 X.



Fig. 17—Fluorescent micrograph showing aggregated human IgG in the mesangial cells of a rat with nephrotoxic serum nephritis, 24 hours following intravenous injection of the aggregates. Note the centro-lobular position and arborization pattern of the deposited protein complexes within the mesangium. The peripheral capillary loops are negative. (Control animals showed much less uptake) (Ref. #57). Magnification 400 X.

The Role of the Mesangium in Glomerular Permeability

The mesangium is a system of cells and intercellular matrix that occupies the central area of each lobule, is enclosed by the GBM, and is separated from the capillary lumen by the endothelium. (Figure 16). (See ref #53 for review of mesangium.) The phagocytic function of this interdigitating system of cells and channels between the cells was first clearly demonstrated by Latta, et al, [54] using particles of thorotrast. Farquhar and Palade [55] demonstrated the uptake of ferritin particles by these cells and suggested that the mesangium might function to clear the lamina rara interna of the GBM of residue collected in the filtration process. Mauer et al.[56,57] have shown that aggregated proteins of various sizes (as heat aggregated IgG) when injected into animals, localize rapidly within the mesangium where they are readily detected by histologic and immunofluorescence techniques. (Figure 17). Using radioactively labelled similar aggregates, it has been possible to construct kinetic curves relating uptake to time following aggregate injection[56]. In the normal rat there is a prompt increase in glomerular uptake followed by a logarythmic decrease in the glomerular content of aggregated IgG reflecting loss or degredation, over a period

of 48-96 hours.

These studies clearly establish a phagocytic function for the mesangium similar to that of the reticuloendothelial system. The mechanism of uptake, degradation, and transport of materials by the mesangium are not known.

When stimulated by mechanisms such as immune complexes deposited between the endothelium and the GBM, mesangial processes can be shown to extend from the centrolobular region around the capillary loop for considerable distances beneath the endothelium. This process has been called interposition of the mesangial cells and is typically seen in membranoproliferative glomerulonephritis[24] (Figure 9), but also occurs occasionally in other forms of glomerulonephritis and in diabetic nephropathy. The mesangial processes apparently lay down new GBM material to give the "splitting" appearance of the GBM seen by silver stains.

Recent studies using particles of colloidal carbon, which are biologically inert and non-digestible, have aided in evaluating these processes.[58] After intravenous injection in rats, carbon particles were found within the capillary lumena at five to 10 minutes and within the mesangium within one hour, by light and electron microscopy. (Figure 18). Carbon appears to enter the mesangial cell region by passing through the endothelium at the mesangial-endothelial interface, into channels between adjacent mesangial cells. These channels are the spaces which normally contain basement membrane-like material, the mesangial matrix. In the carbon injected animal, these potential spaces become channels containing decreased matrix material (more fluid?) and aggregates and particles of carbon. At later time periods the carbon is found within membrane lined vacuoles within the mesangial cell cytoplasm, as a result of phagocytosis by these cells. In these studies the distribution of the carbon was evaluated by serial sacrifice of rats through a total of seven weeks. The concentration of carbon in the mesangium at the periphery of the glomerulus decreased progressively after two weeks, while the concentration within the more central glomerular stalk, the axial pole, the lacis cells, and the juxtaglomerular region increased to reach a maximum at four weeks.

These observations suggest a transport system within the mesangium which slowly moves particles toward the base of the glomerulus. The efferent limb of this system has not been clearly identified, but we are attracted to the possibility that the renal lymphatic system is likely to be involved in removal of material reaching the interstitial space around the base of the glomerulus.

The influence of altered glomerular permeability on mesangial uptake of particles was first recognized by Farquhar, and Palade[59] who gave ferritin to AN nephrotic rats and demonstrated an increased uptake of ferritin into the mesangium as compared to controls. Mauer, et al., have demonstrated a four to five increase in uptake of aggregated IgG by the mesangium of AN nephrotic[56] and nephrotoxic nephritic rats[57]. Similar marked increases in the uptake of injected aggregates have also been recently demonstrated by the mesangium of rats with experimental alloxan induced diabetes[60].

These studies indicate a unique relationship between the filtration surface of the glomerulus and the mesangium. Increased capillary permeability is regularly associated with increased permeability of the mesangium. Pathologic and immunofluorescent studies of kidney biopsy specimens in a variety of renal diseases in man, (reviewed earlier) also support this conclusion, as do numerous investigations of the mesangial uptake of immune complexes in experimental ne-

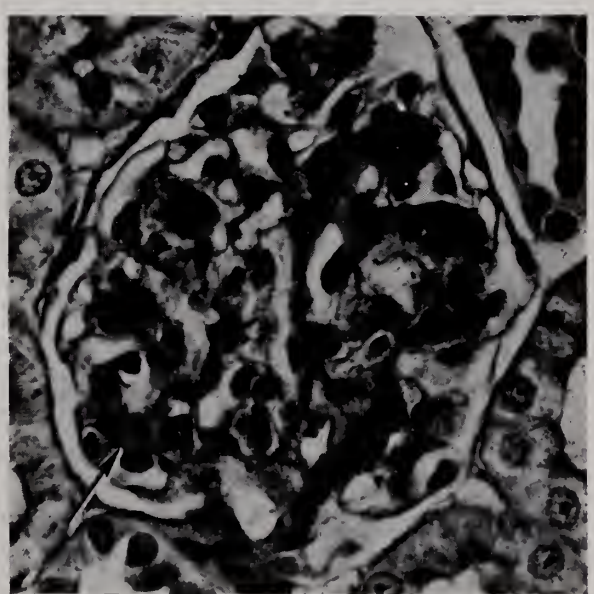


Fig. 18—Photomicrograph of a glomerulus from a rat given an intravenous injection of colloidal carbon, 24 hours earlier. Note the centrolobular position of carbon particles (small black dots) within most mesangial areas (arrow). At this time the basilar area of the glomerulus is free of carbon particles. (PAS stain magnification 600 X).

phritis in animals[61]. The earliest lesion recognized in diabetes mellitus, is expansion in the volume of the mesangium, which is the precursor of intercapillary glomerulosclerosis of Kimmelstiel-Wilson[62]. The pathogenesis of the focal sclerotic lesion and of mesangial hyperplasia, described earlier, in patients with the nephrotic syndrome remains unknown, but likely involves abnormalities of this cell system. Continued exploration of function, biochemistry, immunology and pathology of the mesangial cells in health and in disease will undoubtedly lead to more rational and effective therapy for the nephrotic syndrome, which remains a complex, frustrating, and fascinating enigma of medial practice.

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Lupus Nephritis

JAMES V. DONADIO, JR., M.D.* AND KEITH E. HOLLEY, M.D.†

In patients with SLE and clinical evidence of renal involvement establishing a morphologic diagnosis provides a basis for treatment and prognosis.

THE IMPORTANCE OF RENAL involvement in patients with systemic lupus erythematosus (SLE) was first called to the attention of physicians by Keith and Rowntree in 1922.[1] With percutaneous renal biopsy it is now possible to classify various forms of lupus renal disease.[2,3] Today, the clinician and the pathologist, must work together to formulate proper diagnostic and therapeutic approaches to the patient with lupus renal disease. Some patients with renal disease display a relentless, progressive course but most patients can be treated effectively when early diagnosis is made.

Clinical Diagnosis

SLE is a clinical syndrome of unknown etiology characterized by multisystem involvement, multiple remissions and exacerbations and serologic abnormalities.[4] Our clinical approach to each patient with SLE is to carefully assess renal status (Table 1). If an abnormal urine sediment (in particular, erythrocyte and/or blood casts), reduced renal function and/or the nephrotic syndrome are found, we then attempt to establish a renal morphologic diagnosis. Treatment depends on the findings of renal biopsy. Prospective, long-term study of all patients with lupus renal disease is necessary in order to determine the ultimate outcome of patient and kidney survival.

*Division of Nephrology and Internal Medicine, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
†Department of Anatomy and Pathology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

TABLE I
Systemic Lupus Erythematosus
Evaluation of Renal Disease

1. Urinalysis & urine sediment
2. Quantitation of renal function
3. Measurement of protein excretion
4. Renal morphology

Renal Morphologic Diagnosis

General

The morphologic classification of lupus nephritis is based primarily on glomerular changes. McCluskey[3] has based his classification primarily on the extent of involvement within the biopsy rather than the severity of the individual glomerular lesion. He classifies the lesions of lupus nephritis as *Focal Lupus Nephritis* or *Diffuse Lupus Nephritis*. Focal denotes involvement of only a portion of glomeruli present in the biopsy (i.e. 10-20%). This involvement may be limited to one or two lobules (segmental) or involve all

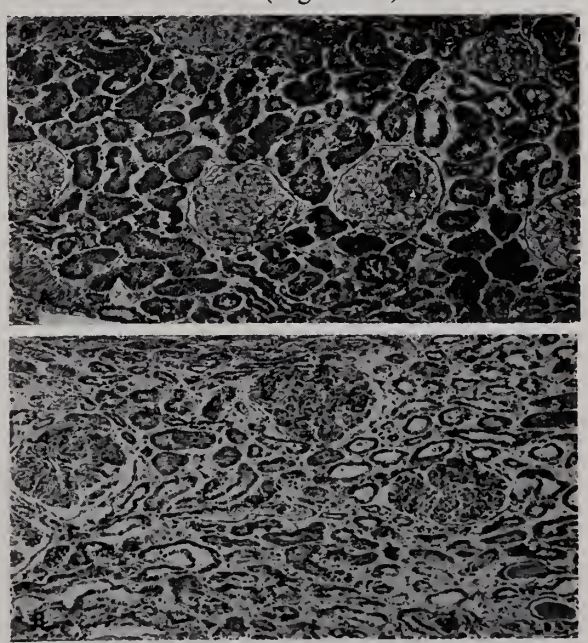


Fig. 1—(Top) Example of Focal Lupus Nephritis. Note focal-segmental hypercellularity with karyorrhexis and normal adjacent glomeruli. (Bottom) Example of Diffuse Lupus Nephritis. Note generalized glomerular hypercellularity, tubular changes and interstitial edema. Hematoxylin and eosin X 50.

lobules of an individual glomerulus. Many glomeruli will appear normal. In the diffuse form, the majority of glomeruli show involvement (i.e. 80-100%) although the degree of involvement of individual glomeruli is often variable. In the classification of Pirani and Manaligod[2] most of these lesions would be termed *Active Lupus Glomerulonephritis (nephritis)* (Figure 1).

Pirani and Manaligod[2] further defined a group of lupus glomerulonephritis that show morphologic features of "inactivity." Changes indicating "activity" included cellular proliferation (including crescents), fibrinoid deposition (immune complexes plus fibrin), karyorrhexis, necrosis, presence of polymorphonuclear leukocytes (PMN's) in the glomerular lesions, hyaline thrombi and arteriolitis.

In contrast "inactive" lesions included the absence of most changes noted in active lesions with mesangial hypercellularity persisting to varying degrees yet to a lesser extent than when the lesion was "active." Additional features of inactivity included "membranous" thickening of the capillary wall, glomerular scarring and varying degrees of tubular atrophy and loss, scattered interstitial scarring and chronic inflammatory infiltration.

Both McCluskey and Pirani describe a less common form of lupus nephritis, namely, *Lupus Membranous Glomerulonephritis (nephropathy).* This lesion has similar morphological characteristics as idiopathic membranous nephropathy. The capillary walls are uniformly thickened, cellularity is generally normal, and subepithelial deposits and "spiking" of the glomerular basement membrane are noted on PAS methenamine silver stained-sections (Figure 2). Electron microscopy shows primarily subepithelial deposits and less commonly subendothelial and mesangial deposits. Immunofluorescent histology shows granular deposits of immunoglobulins plus complement components (C3 and C4) along the capillary wall.

Specific Features (Figure 3)

The pleomorphic nature of the glomerular changes (when compared with other forms of glomerulopathies) is striking. The most "characteristic" glomerular lesion is one that is segmental or local (one or two lobules) and exhibits the following features: *Cellular proliferation* and *swelling* (mesangial, endothelial); *thickening* of the *capillary wall* (fibrinoid deposition—wire loops); *karyorrhexis; increase* in *mesangial matrix* (deposits); *swelling* of *visceral* and *parietal epithelial cells* (frequent cellular and cytoplasmic adhesions to capsule). Frequently seen within these lesions are PMN's (usually only one or two) and hyaline thrombi. Hematoxyphil bodies and diffuse crescent formation are not frequently observed.

Electron microscopic studies reveal dense deposits ("fibrinoid") along the subendothelial aspect of the basement membrane and within the mesangium (Figure 4A). Subepithelial deposits are also present and are the predominant lesion noted in the diffuse membranous form of the disease. Immunofluorescent histology shows granular deposits of IgG, IgM, C3 and to lesser extent IgA along the capillary walls and within the

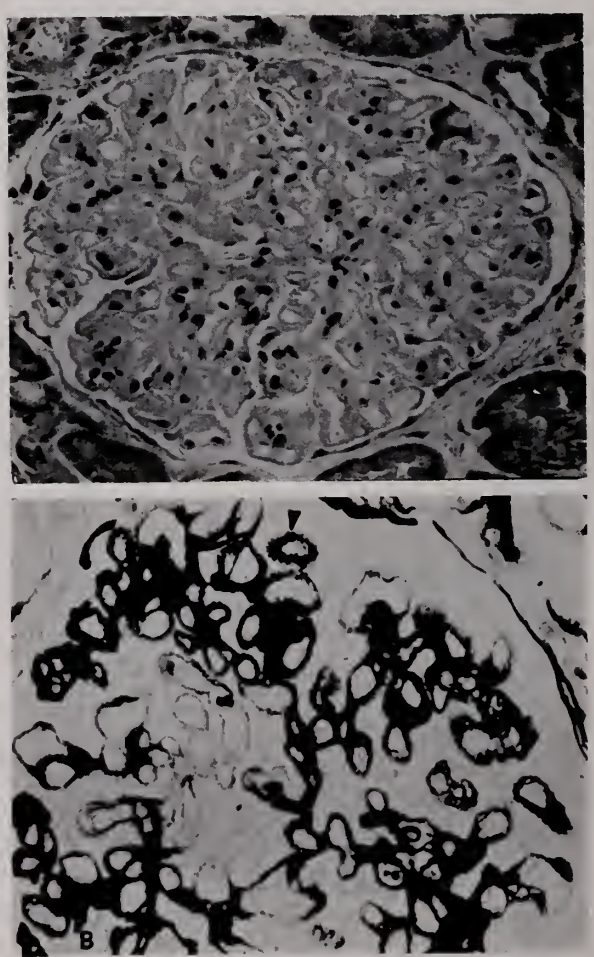


Fig. 2 Lupus Membranous Nephropathy. (Top) Diffuse thickening of capillary walls, normal or decreased cellularity and decrease in diameter of capillary lumens. H&E X 400 (Bottom) Thickened basement membranes with silver positive projections—spikes (arrowhead). Jones PAS methenamine silver stain X 400.

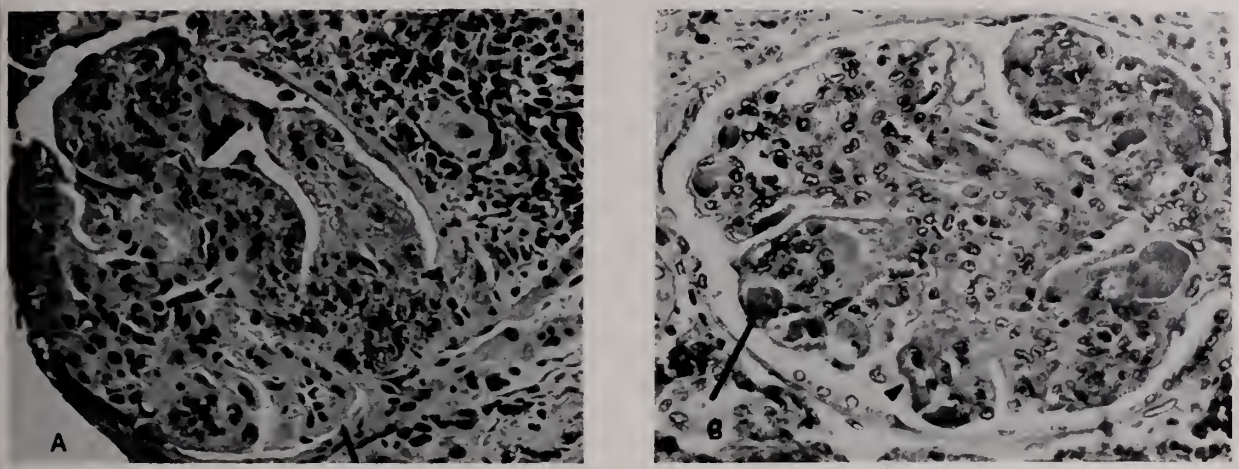


Fig. 3—(A-left) Glomerulus shows extensive involvement. Specific features include cellular increase with absence of capillary lumens, karyorrhexis, fibrinoid thickening of capillary walls (thin arrow), hematoxyphil material (arrowhead) and involvement of juxtaglomerular arterioles. H&E X 250. (B-right) Diffuse glomerular involvement with many hyaline thrombi (thin arrow) and subendothelial deposition of immune complexes (fibrinoid) (arrowhead). H&E X 250.

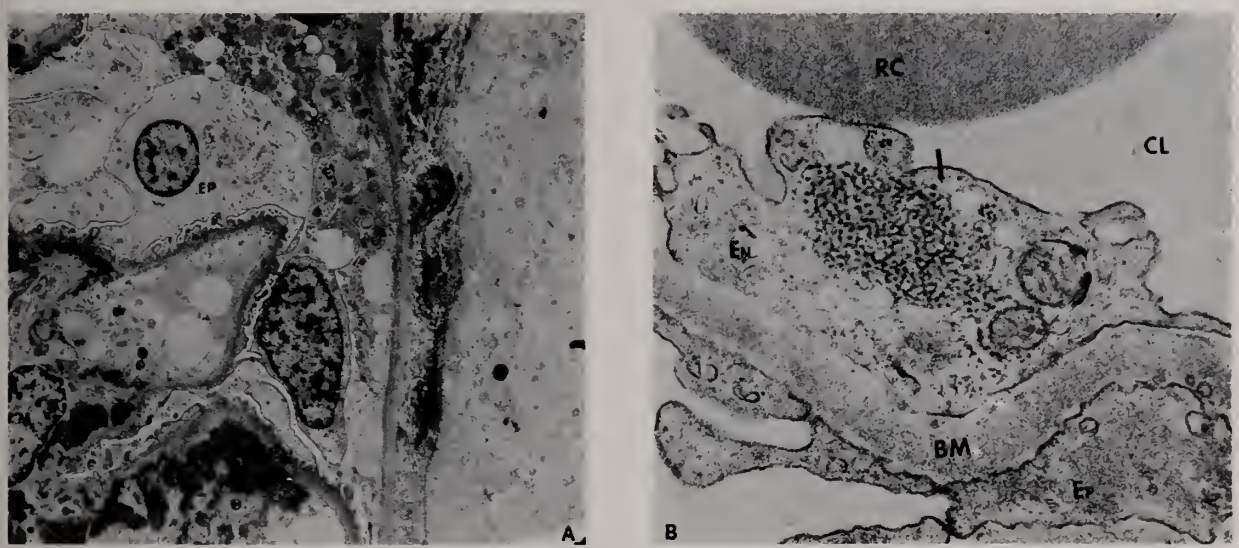


Fig. 4—Lupus glomerulonephritis: (A-left) Note deposits (d) of fibrinoid—immune complexes in subendothelial space and mesangium. BM = basement membrane, CL = capillary lumen, EP = visceral epithelial cell, M = mesangial cell and BC = Bowman's capsule. Original magnification X 24,000. (B-right) Complex tubular structures (arrow) in endothelial cell cytoplasm in lupus nephritis. RC = red blood cell, EN = cytoplasm of endothelial cell. Original magnification X 42,000.

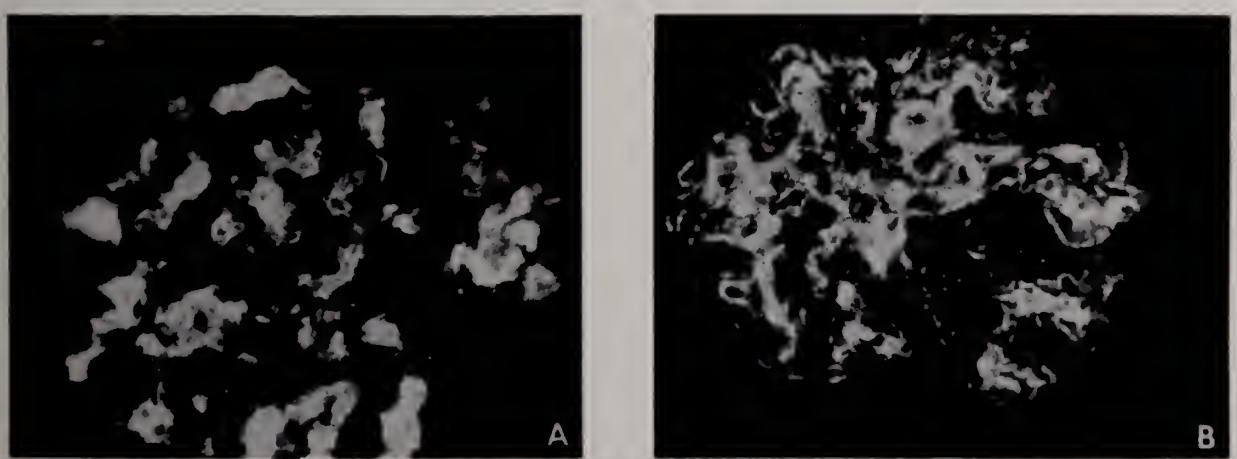


Fig. 5—Immunofluorescent history showing presence of IgG immunoglobulin in the glomerulus of patients with lupus nephritis. (A-left) Predominant mesangial pattern with focal linear staining of capillary walls. X 250. (B-right) Diffuse granular staining of capillary walls. X 250.

mesangium (Figure 5). The immunofluorescent patterns in lupus nephritis consist of both Class I and Class II Immune Complex Deposit Disease as proposed by Germuth.[5]

Fibrinoid Deposition—Fibrinoid Necrosis

The thickening of the capillary wall with formation of the "wire loop" is due to an accumulation of material that on hematoxylin and eosin-stained sections is homogeneous, acellular and brightly eosinophilic. A chemical homogeneity of this material cannot be assumed. In lupus nephritis immune complexes comprise a large part of the fibrinoid. Deposits are present not only in a subendothelial location but also in the mesangium and in a subepithelial location. Pirani[2] has given an excellent review of this topic.

Hyaline Thrombi

Pirani[2] points out that many hyaline thrombi are composed of the same material present in the subendothelial deposits, e.g. fibrinoid. In some sections this material may appear loose in the capillary lumen; however, additional sections may show its attachment to the endothelial surface of the capillary wall. Other hyaline thrombi are not attached; however, they are presumably not freely circulating (e.g. systemically). They may represent detached masses of fibrinoid.

In some cases of lupus nephritis intravascular coagulation may occur and small fibrin and platelet thrombi may also be present. These thrombi can usually be distinguished from hyaline thrombi on close microscopic inspection.

Finally some cases of lupus nephritis may be associated with mixed cryoglobulinemia and masses of cryoglobulin may be present in the glomeruli. Usually these thrombi appear somewhat larger and irregular in shape than that in lupus nephritis not associated with cryoglobulinemia.

Karyorrhexis, Proliferation and Hematoxyphil Bodies

Fragmentation of intracapillary nuclei is a common feature of the active-segmental lesion. Proliferation of mesangial and endothelial cells is always present and frequently cellular adhesions or small crescents form between tuft and Bowman's capsule. Pirani[2] has pointed out the difficulty of defining disruption of capillary walls particularly on light microscopy. Usually these lesions are associated with varying degrees of fibrinoid deposition. Less commonly the individual lesion can be associated with necrotizing features that include deposits of fibrin and may be indistinguishable from glomerular lesions associated with various forms of vasculitis. Hematoxyphil (or hematoxylin) bodies, while specific, are seen in their conventional form in 5-8% of the lesions. When hematoxyphil material is searched for and identified by criteria of Pirani,[2] or Heptinstall,[6] its incidence may be increased to near 20%. Tissue fixation, staining procedures, number of sections examined influence the incidence of hematoxyphil material.

Arteries

True arteriolitis or arteritis is uncommon in lupus nephritis. In some cases fibrinoid will be deposited in a subendothelial location in juxtaglomerular afferent arterioles. It is unusual for an active inflammatory cellular infiltrate to be present in the wall of an arteriole or small artery. In those cases associated with intravascular coagulation, or more commonly hypertension, intimal fibroplasia will be noted in small arteries and arterioles.

Tubules and Interstitium

Tubular lesions vary. It is common to have focal areas of active tubular necrosis and associated with a mixed inflammatory cellular infiltrate. Plasma cells may be numerous.

Electron microscopic examination has demonstrated tubular structures in the cytoplasm of glomerular endothelial cells (Figure 4B). These virus-like structures are found in 80-90% of patients with lupus nephritis. They have also been noted in 10-15% of cases with renal disease not associated with systemic lupus erythematosus as well as being present in cells other than glomerular endothelium.[7]

Clinicopathologic Correlations and Treatment

Our remarks concerning treatment concern only the patient with renal involvement. In general, early, less destructive renal lesions are amenable to most treatments, while late, destructive and diffuse glomerular lesions respond unpredictably to any treatment.

In terms of the morphologic classification given in Table 2 those patients with *glomerulitis* do not require intensive steroid or other cytotoxic drug

treatment. Usually, the patient has normal renal function, minimal proteinuria and perhaps only an abnormal urine sediment. The glomerular lesion usually remains stable and does not progress into a more active form of glomerulonephritis. Active glomerulonephritis may evolve in a small number of patients making it advisable that all patients with glomerulitis have regular urine sediment and renal function examinations as part of their followup assessment.

TABLE 2
The Kidney in Systemic Lupus Erythematosus
Histopathologic Classification and Description

Classification	Description
Glomerulitis	Minimal morphologic changes in a few glomeruli; mainly mesangial proliferation and/ or matrix increase.
Active Glomerulonephritis	Intracapillary cellular proliferation, capillary wall thickening (fibrinoid deposition—"wire loops"), karyorrhexis, masangial thickening (deposits), visceral and parietal cell swelling, hematoxyphil bodies, tubular—interstitial changes; involvement may be segmental (1 or 2 glomerular lobules) in some glomeruli—"focal nephritis"—or it may be diffuse (2 or more lobules) in all glomeruli—"diffuse nephritis."
Membranous glomerulopathy	Thickened capillary walls, mesangial thickening; subepithelial deposits and basement membrane "spikes."

Lupus membranous nephropathy represents a small subgroup of renal lesions found in patients with SLE. In studies in which renal histology has been well-defined, there are discrepancies in the incidence and clinical course of such patients.[8,9] Most authors, however, report a less than 10 percent incidence among patients who have received renal biopsy and a favorable prognosis with respect to preservation of renal function. The clinical renal manifestation is either the nephrotic syndrome or persistent proteinuria without other features of the nephrotic syndrome.

In adults, membranous nephropathy is generally found in the patient who has had well-established SLE for months or years, and who may or may not have received prior steroid or other cytotoxic drug treatment. In fact, such treatments do not influence either the lesion or proteinuria. As in the case with minimal glomerular changes (glomerulitis), patients with lupus membranous nephropathy should be treated only with respect to those measures required to control the systemic manifestations of the disease.

Active lupus glomerulonephritis comprises the largest subgroup of renal lesions of SLE. Those cases with more extensive glomerular changes are more likely to have clinical renal changes. These include glomerular insufficiency, nephrotic syndrome and hematuria, and casts of all types, especially erythrocyte, in the urine sediment.

The importance of establishing a lesion of active lupus nephritis as early as possible cannot be overstated. Early diagnosis provides the best chance to treat the disease and improve or stabilize the clinical renal abnormalities.

Adrenocorticoids have been used most extensively in various forms and dose regimens.[10-12] When active glomerulonephritis is present, primary treatment has been with high doses of steroids unless otherwise contraindicated. The total duration and dosage of steroid treatment varies, of course, from patient to patient and according to the clinical course. The object in each instance is to achieve disease control without trading such control for toxic treatment effects.

After initial treatment, and when the dose of prednisone is in the range of 10-15 mg./day, recurrent systemic symptoms may emerge. During such systemic flares careful assessment of immunologic activity, renal function, protein excretion and urine sediment must be made. If recurrent lupus nephritis can be excluded, control of systemic manifestations should be undertaken by conventional measures other than with high doses of steroids. These measures include extra rest, regular use of salicylates, skin care, antimalarial drugs, and sometimes small increments in the dosage of steroid.

Cytotoxic Drugs

Because of inadequate control of systemic symptoms, progressive renal disease and toxic complications occurring in some patients treated with steroids, cytotoxic drugs have been tried. Treatment studies with various cytotoxic drugs and short-term patient follow-up have resulted in claims that these agents are useful when added to steroids.[13,14] In many reported studies, there have been no matched control groups and assessment of renal disease has not been uniform.

In addition, and perhaps of greatest importance, there is great difficulty in attempting to

control treatment of a variable disease process such as SLE. Thus, claims that various cytotoxic agents are beneficial to lupus patients with renal disease leave much to be desired. Furthermore, and basic to the issue, information is not available concerning long term effects of these agents especially with respect to preservation of renal function, patient survival and toxic manifestations.

Evaluation of the use and effectiveness of cytotoxic agents in SLE is under current study in many medical centers. No one agent has proved more efficacious than another in controlling either severe systemic or renal manifestations. Cytotoxic drug treatment may be potentially useful in: (1) Progressive or recurrent major systemic manifestations, including renal disease, in spite of adequate steroid treatment; (2) Major proven steroid toxicity, for example, aseptic necrosis of a femoral head, gastrointestinal bleeding, repeated serious systemic infections, thromboembolic phenomena, documented steroid psychosis, steroid myopathy and diabetes mellitus.

Renal Morphologic Activity Versus Severity

Our final comments concern renal disease activity and severity. These two terms may have different meanings in a given patient's renal biopsy. Activity refers to current, ongoing inflammatory changes affecting glomeruli, tubules and interstitium resulting from deposition of circulating immune complexes primarily in glomerular capillaries. Severity indicates the degree of renal involvement, i.e., its extent, and includes chronic and irreversible changes of fibrosis.

In assessing patients with lupus glomerulonephritis, we employ a semi-quantitative analysis of renal biopsy tissue to assess morphologic activity.

TABLE 3
Biopsy Activity Score

	Grade	• f	Score
Glomeruli			
Proliferation			
Intracapillary	2+	2	4
Extracapillary	0		
Karyorrhexis	2+	2	4
Necrosis	2+	2	4
Fibrinoid	1+	2	2
Hyaline thrombi	0		
Hematoxylin bodies	0		
Interstitium	1+		1
Tubules	1+		1
Vessels	0		
	"moderate activity"		16

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In a reported study, we evaluated patients with active lupus glomerulonephritis in terms of treatment response using prednisone alone or combined prednisone and azathioprine.[15] To make treatment assessment comparable, patients were treated in each group who had comparable renal lesions as judged by our analysis of morphologic activity. Features of activity are shown in a sample scoring of a biopsy (Table 3).

These changes are most likely to be influenced by adrenocorticoid or cytotoxic drugs, that is, at the site of inflammation, or perhaps they influence immune complexes that are mediating glomerular injury. Lupus glomerulonephritis in which mainly chronic changes are demonstrated is not likely to be influenced substantially by either prednisone or cytotoxic drugs. Glomerular sclerosis, interstitial fibrosis and tubular atrophy are indicative of previous inflammatory activity. To our knowledge, there are no currently available drugs which favorably effect this stage of the process. Obviously, from a therapeutic and prognostic standpoint, early diagnosis of active glomerulonephritis is a most critical task.

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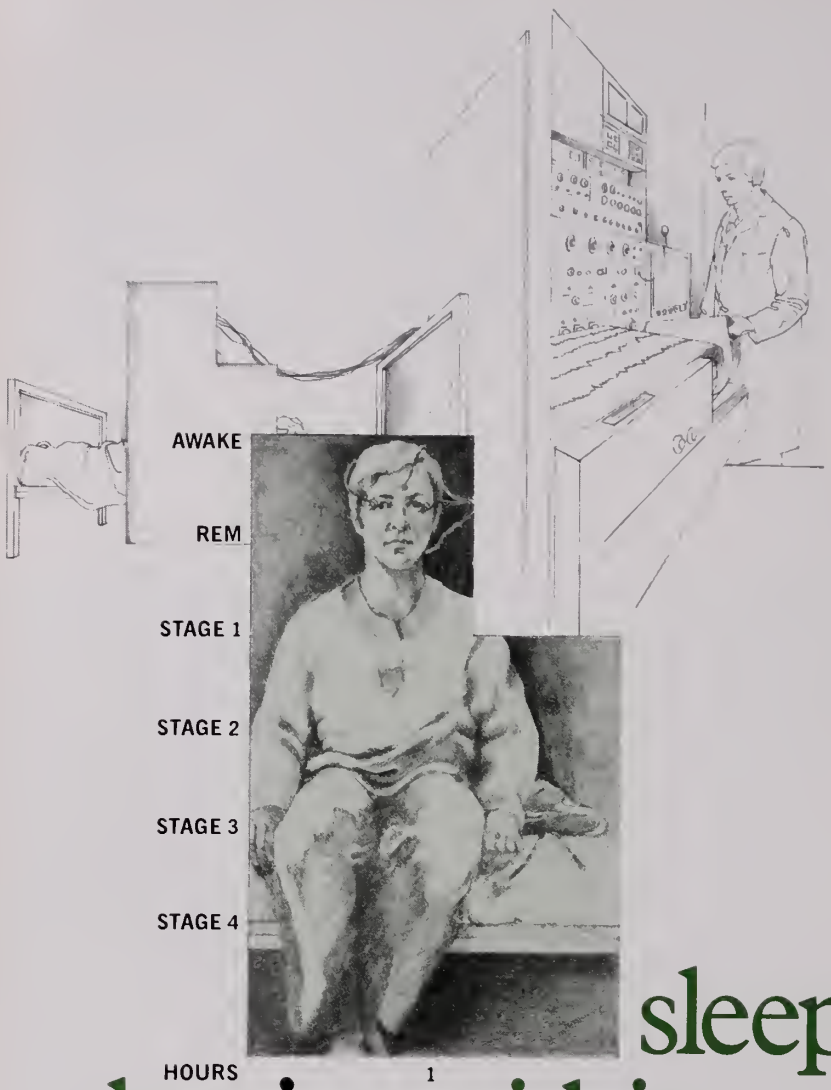
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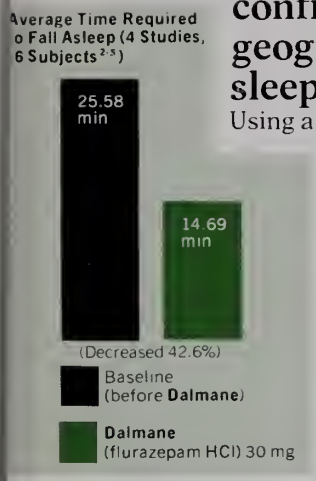


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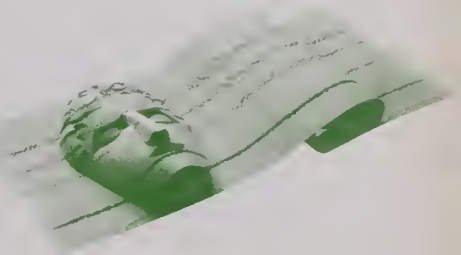
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IMPORTANT INFORMATION: *This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for meperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL* IS NOT *AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.*

Indications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

Contraindications: In children less than 2 years, due to the decreased safety margin in younger age groups, and in patients who are jaundiced or hypersensitive to diphenoxylate HCl or atropine.

Warnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced hepatic disease or abnormal liver function tests, because of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

*Dosage and administration: **Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

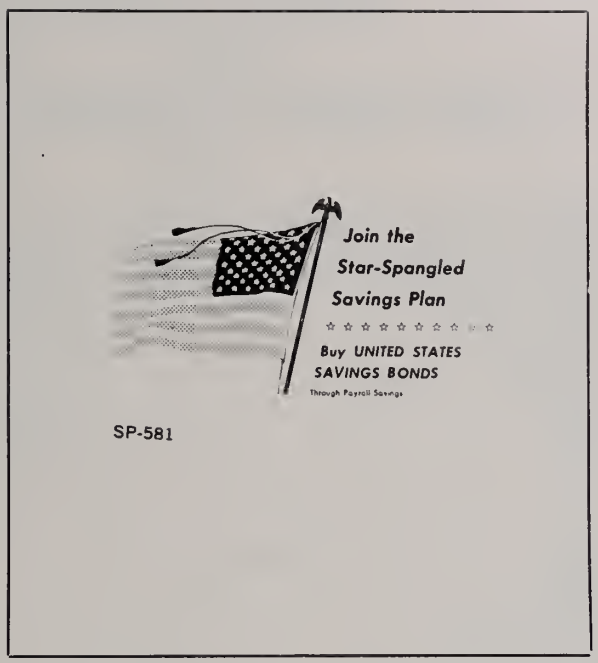
Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid,* 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

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Editorials

Clinical Relevance of Laboratory Output

MSCP's Annual Spring Program

In recent years, more and more of the pathologist's time is spent in keeping abreast of new developments and in evaluating, adapting and setting up new laboratory techniques. This raises the possible danger that the laboratory professionals may become too engrossed in laboratory procedures and, as a consequence, run the risk of losing clinical perspective. For the clinician, the price of our progress in understanding of disease states has been the taxing of an already overcommitted schedule with a burgeoning body of laboratory knowledge.

The possibility of a growing gap between the laboratory world and bedside medicine is a particularly serious problem. To prevent or resolve this problem communication channels must deliberately be built to conserve the clinical relevance of laboratory output. The laboratory must maintain a clinical awareness and the clinician a laboratory awareness. An effective means of disseminating integrated medical knowledge is through presentations by experts that review, update and place in perspective the current knowledge of a well-defined disease state.

To accomplish these objectives the Minnesota Society of Clinical Pathologists has recently changed the format of its annual Spring Program. Well-defined disease entities are chosen and discussed in counterpart by pathologists and clinicians who are experts in the particular field. The success and the enthusiasm with which these programs have been received have prompted us to publish the proceedings of these meetings.

The advances made in the past few years in the study of nephrology and nephropathology were the timely topics of this year's Spring Meeting. The articles on these subjects in this issue of Minnesota Medicine were derived directly from the presentations given at that time. All the contributors are practicing physicians in the state of Minnesota. We are particularly pleased and consider it most appropriate that our own state journal—Minnesota Medicine—has agreed to publish these proceedings.

Each author has assumed the doubly onerous task not only of preparing a lecture but also committing it to paper for publication. I would like to express my personal thanks as well as the appreciation of our entire Society to all of the contributors for this splendid manifestation of service to clinical medicine and to pathology.

Michael B. O'Sullivan, M.B., B. Ch., B.A.O.*
Guest Editor

*Chairman, Program Committee, Minnesota Society of Clinical Pathology.

Fractures of the Orbit

Fractures of the walls of the orbit occur either as a blowout-type or as a part of more severe injury to the midfacial region. Various studies have reported that between 25 and 40% of patients who sustain such fractures also suffer severe injury to the globe. All patients who have sustained fractures of the orbital walls should be examined by an ophthalmologist.

Assuming that the immediate needs of the injured patient have been attended to, the ophthalmologist should establish whether or not the globe has been injured seriously. Serious occult injury can be overlooked. With the integrity of the globe established, ocular motility should then be evaluated.

When diplopia is present, most patients can be observed safely for 10 to 14 days. During this time, serial diplopia field testing can be done. If such testing reveals that ocular motility is progressively improving, the period of observation could be extended. As injury to the soft tissue subsides, many patients regain binocularity without the need for surgery.

The bony orbit and its contents are a complex and delicate part of the anatomy upon which surgical intervention should not be undertaken lightly. If there is one ophthalmologic indication for orbital surgery after trauma, it is the presence of persistant diplopia in a functionally important field of gaze.

In the more severe types of midfacial fractures, a multidiscipline subspecialty approach may be required. The ophthalmologist should be a member of the team when ophthalmic implications exist. If the implications are only ophthalmic, the patient should be managed by the ophthalmologist. Surgery would be carried out best by an anterior orbital approach rather than by a combined approach, and should be done only after appropriate evaluation and observation indicate the need.

The case reported by Slack* of a patient who suffered blindness after repair of an orbital floor fracture, in spite of its unfortunate outcome, serves to remind us of several important aspects of such fractures and their management.

Roger W. Neault, M.D.†
Rochester, Minnesota

*See page 958, December issue, Minnesota Medicine.
†Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

Psychiatric Consultation in a General Hospital

Dr. John Scanlan's paper describing psychiatric consultation in a general hospital is both timely and important, since it is likely that the consultation-liaison area will become the most rapidly growing field in psychiatry. As we all enter a period of expanding peer review, we become increasingly aware of the need to do everything necessary to treat the whole patient during any given hospitalization and are more likely to consider the need for all possible consultations as we devise an initial treatment plan. Some of the data presented should be of as much interest to those making psychiatric referrals as it is to those who answer them. Surgery referred 22 of its 1,985 admissions during the period studied, while medicine asked for consultation in 103. If we assume that all 63 patients who attempted suicide were admitted to medicine, and deduct that number from the total referred, we find that service referring another 40 of its 1,157 admissions, asking for consultation four times as often on its nonsuicidal patients as did surgery. We can well ask whether the difference lies in the patients or ourselves, and hope that psychiatric consultation continues to develop on all hospital services.

Richard W. Anderson, M.D.†
Minneapolis, Minnesota

*Minnesota Medicine 57:922, November, 1974.
†Professor, Coordinator of Clinical Services, Department of Psychiatry, University Hospitals, Minneapolis.

Sexual Attitude Reassessment

SEX EDUCATION AND courses or seminars on human sexuality continue to be a sensitive and controversial issue even among health professionals.

The article by Held et al.* helps acquaint our medical community with the nature, reasons for establishing, and results and apparent usefulness of the seminar developed at the University of Minnesota Medical School. The seminar has become an interdisciplinary endeavor. Thus the seminar provides an open approach to sexuality.

Held et al. report most participants felt the seminar has been "beneficial."

I would agree with the authors that *the attitudes* of a professional toward human sexuality is of primary importance in effective counseling. Being comfortable with one's own sexuality, being aware and accepting of the concerns, and feelings of others is conducive to more comfort and ease in discussing sexual issues and problems. These attitudes give the professional better motivation to obtain more knowledge concerning human sexuality. He would then be more comfortable, open and willing to use this knowledge in the counseling of others. Thus a truly scientific attitude of openness in sexuality is a prerequisite for a professional to be a knowledgeable and effective practitioner.

The SAR seminar seems to be of significant value in the medical school curriculum if it does provide openness concerning human sexuality. One would only hope that the seminar itself would continue to be open to new insights, modifications and further search for more complete understanding of human sexuality without becoming dogmatic about "pseudo-openness."

Ilgvars J. Nagobads, M.D.
Minneapolis, Minnesota

*Minnesota Medicine 57:925, 1974.

Popliteal Artery Arteriosclerotic Aneurysm

CONTRARY TO THE current report of Toledo-Pereyra and Sako,* in which they mention that only 11 patients with popliteal artery aneurysms were seen at the Minneapolis Veterans Administration Hospital over a 17-year period, the relative incidence of popliteal artery arteriosclerotic aneurysms is increasing because of both the continued extension of life expectancy into the age group susceptible to arteriosclerotic changes and the decreased incidence of syphilis in the general population.[1,2] As suggested by Toledo-Pereyra and Sako, the precise incidence of aneurysms in the popliteal artery is unknown. This lack of information reflects the fact that the popliteal area is too infrequently studied during routine physical examination and is seldom exposed at autopsy.

Of 152 patients with 233 popliteal artery aneurysms seen at the Mayo Clinic[2] between 1961 and 1968, 231 aneurysms were arteriosclerotic. The incidence of associated cardiovascular disease also was high, with 46 patients (30%) giving a history of either myocardial infarction or cerebral vascular accident.

The diagnosis of popliteal artery aneurysm invariably is made by inspection and palpation of the popliteal space. Roentgenograms of the popliteal space demonstrate a soft-tissue mass in more than 50% of the patients, and calcification of the aneurysm occurs in 25%. Although arteriography is seldom necessary to confirm the diagnosis of an aneurysm, it is important in determining the status of the arterial circulation both proximal to and distal to the aneurysm and thus should be done before the operation whenever possible.

When considering the management of a patient with a popliteal aneurysm, it is important to be aware of the natural history of the aneurysm. Contrary to Toledo-Pereyra and Sako's report, in which they mentioned that they had rarely performed amputations for an undetected aneurysm, the experiences of most observers would suggest that asymptomatic popliteal artery arteriosclerotic aneurysms eventually either thrombose or embolize.[3] This leads to distal arterial obstruction capable of producing all degrees of ischemia from claudication to gangrene. Of 94 popliteal artery aneurysms not treated surgically between 1961 and 1968 at the Mayo Clinic, 27 (29%) developed complications which led to amputation in three limbs (3%). In addition to thromboembolic phenomena, other complications included pain in

*See page 947, December issue, Minnesota Medicine.

the popliteal space, thrombophlebitis, and venous obstruction. Rupture of the aneurysms did not occur.

Surgical treatment of a popliteal artery aneurysm should be instituted for all patients whose life expectancy is not reduced by other associated cardiovascular disease. Ideally, the operation should be performed while the aneurysm is still asymptomatic.

As pointed out by Toledo-Pereyra and Sako, the surgical procedure is choice of resection of the aneurysm and restoration of arterial anastomosis, graft interposition, or bypass of the aneurysm. When autogenous saphenous vein is available, it is the graft of choice. Seventy-five percent of 20 patients treated at the Mayo Clinic with saphenous vein grafts were asymptomatic or improved for a follow-up period averaging 1.6 years, with equally good results for both bypass and interposition grafts. In the absence of a suitable vein, use of a knitted Dacron prosthetic graft is a reasonable alternative. Seven of 11 patients treated with Dacron grafts were improved for an average follow-up period of 2.5 years after surgical treatment. If arteriograms made before operation fail to demonstrate distal arterial flow, the popliteal space should be explored, because patent vessels often can be found. In the unlikely event that it is not possible to establish direct arterial flow, the aneurysm should be resected and lumbar sympathectomy should be performed.

Peter C. Pairolero, M.D.*
Rochester, Minnesota

*Section of Thoracic and Cardiovascular Surgery, Mayo Clinic.

References

1. Gifford RW Jr, Hines EA Jr, Janes JM: An analysis and follow-up of one hundred popliteal aneurysms. Surgery 33: 284, 1953.
2. Wychulis AR, Spittell JA Jr, Wallace RB: Popliteal aneurysms. Surgery 68:942, 1970.
3. Crawford ES, DeBakey ME: Popliteal artery arteriosclerotic aneurysm (editorial). Circulation 32:515, 1965.

Cover Photo

"Snowshoeing"

Dr. Julien V. Petit is a 57-year-old physician practicing internal medicine in Minneapolis. His hobbies are photography, skiing, collecting Indian artifacts particularly Kachina dolls.

The cover photograph was taken with a Pentax Spotmaster Camera on KII film several years ago while Dr. Petit and his wife were spending a few days at Northernaire Resort in Wisconsin.

We are told the lady in red is Dr. Petit's wife.

Minnesota Medicine

MINNESOTA MEDICINE is interested in publishing personal items about Minnesota physicians. If you have a personal item, please submit it to: The Editors, MINNESOTA MEDICINE, 375 Jackson St., St. Paul 55101.

MINNESOTA MEDICINE encourages the sending of dates and places of meetings to the Editors for publication in the Journal.

Annual Meeting
Minnesota State Medical Association

May 22-23, 1975

IF THERE IS one thing to be learned from this year's Annual Meeting, it is that today's physician can never stop learning. This year's meeting, the Association's 122nd, reflects our growing concern with the new Continuing Medical Education (CME) requirements. This increased emphasis on CME does not mean that the social aspects of our meeting will be overlooked. It does mean that along with your golf clubs and after-six wear, you'd better pack a notebook and your CME report form!

A stimulating scientific program of seminars and a general session for 350 will be held simultaneously morning and afternoon both Thursday and Friday. Because of their exclusiveness in numbers (limited to 50 or 100) and subject matter, seminars will require pre-registration while the general sessions covering broader topics will be open to all. This format offers six full hours teaching time per day with refreshing and informative 30-minute exhibit breaks morning and afternoon. In addition to our state specialty group presentations, the program will feature internationally known guests and lecturers in the field of medicine.

As a unique and pleasurable close to the two-day session, a "Bavarian Beer Seminar" will be held Friday afternoon. While munching Bratwurst and enjoying German beer, members and their wives can enjoy one another's camaraderie in the luxurious St. Paul Hilton, 1975 meeting site.

The Hilton Hotel and the city of St. Paul will be extending a warm welcome while offering members an array of social, leisure, art and shopping facilities. More on St. Paul and the exciting 1975 program in our next report. Until then, Aufwiedersehen!

Robert D. Semsch, M.D., Chairman
Scientific Assembly Subcommittee

In compliance with the recommendation of the 1974 MSMA House of Delegates, the Scientific Assembly Subcommittee is now a permanent Subcommittee of the Committee on Medical Education. Two meetings have already been held and plans are well underway for the 1975 Annual Meeting. The Scientific Assembly Subcommittee is composed of the following members:

Chairman—Robert D. Semsch, M.D.

Ex-officio Members—Barnard Hall, M.D., President, MSMA; G. R. Diessner, M.D., President-Elect, MSMA; Harold W. Brunn, Executive Secretary, MSMA; Douglas Fenderson, Ph.D., Director, Department of Continuing Medical Education, U of M; Paul F. Bowlin, M.D., Chairman, Accreditation Subcommittee.

Committee Members—H. P. Van Cleve, M.D., Chairman, MSMA Committee on Medical Education; Harley Racer, M.D., Past Chairman, Scientific Assembly Committee; John Mayne, M.D., Second Past Chairman, Scientific Assembly Committee; Donald E. Roach, M.D., President-Elect, Ramsey County Medical Society (Host Society); Richard Chilgren, M.D., University of Minnesota; Martin Adson, M.D., Mayo Clinic; Robert F. Avant, M.D., Minnesota Academy of Family Physicians; Stuart V. Thorson, M.D., Minnesota Academy of Family Physicians; Josiah Fuller, M.D., Minnesota Chapter, American College of Surgeons; John Delahunty, M.D., Minnesota Chapter, American Academy of Pediatrics; John Anderson, M.D., Member-at-Large, MSMA; Robert Cumming, M.D., Member-at-Large, MSMA; Erick Y. Hakanson, M.D., Minnesota Obstetrical and Gynecological Society; John M. Burns, M.D., Chairman, Local Arrangements Committee.

Continuing Medical Education

January-February

East Central Minnesota Medical Society

February 16 through 23, 1975, Steamboat Springs, Colorado.

Everyday problems and family practice of the office with specific subjects in GYN, ENT, gastroenterology and psychiatry. The AAFP credits are requested, it's open to all physicians but especially the family practitioners. Vast capacity of the meeting hall is approximately 40.

Contact: Carlton R. Erickson, M.D., Chisago Lakes Medical Center, P.A., Chisago City, MN 55013.

University of Minnesota

Registration information: Office of Continuing Medical Education, University of Minnesota, Box 293, the Medical School, Minneapolis 55455, or by phone (612) 373-8089.

Courses offered are:

Perinatology—February 22, 1975

Of interest to physicians whose practice includes management of pregnancy and/or the newborn. The course will emphasize conditions that increase risk of fetal distress and growth retardation of the newborn.

Human Sexuality for Physicians and Other Health Professionals—February 14-16, 1975

Emphasizes understanding the range of human sexual behavior, the need for accurate and complete information, and methods of handling problems of sexual adjustments encountered in medical practice. Group discussion techniques are included to help clarify attitudes and values which impinge on effective clinical counselling.

Practical Otolaryngology—February 24-26, 1975

Features a review of current topics, elective workshops and an elective third day of clinical practice. Emphasis has been placed on history, physical diagnosis and techniques in otolaryngology. Plenary sessions, each morning, will present a general discussion on practical otolaryngology. Afternoon sessions will consist of demonstrations and discussion-workshops which can be selected according to the interest of the registrant.

Minnesota Urological Society

Pyelogram Conference, 6:00 P.M. on January 17, February 21 and March 21, at the Marriott Inn, Bloomington. All day spring seminar on April 19, also at Marriott Inn. Contact: Doctor A. S. Cass, St. Paul-Ramsey Hospital, St. Paul.

Metropolitan Medical Center

Neurology

Conferences, Fridays, 8:30 a.m., Center Building, Conference Room, 900 So. 8th St., Minneapolis. Contact: Mary J. Donner, Metropolitan Medical Center—338-7744.

Audio-Visual Network for Continuing Education

9:00 a.m. in Doctor's Lounge, second Tuesday of each month, 900 South 8th Street, Minneapolis. Contact: Margie Knutson, Metropolitan Medical Center, 338-7744.

Tumor Conference—Cancer

Every Monday except if a holiday. 12:00 noon, 900 South 8th Street, Lower Level Conference Room. Contact: Dr. Lyle J. Hay, MMC, 338-7744.

American Diabetes Association of Minnesota and Department of Medicine, University of Minnesota, Veterans Hospital

Place: Veteran's Hospital, Minneapolis.

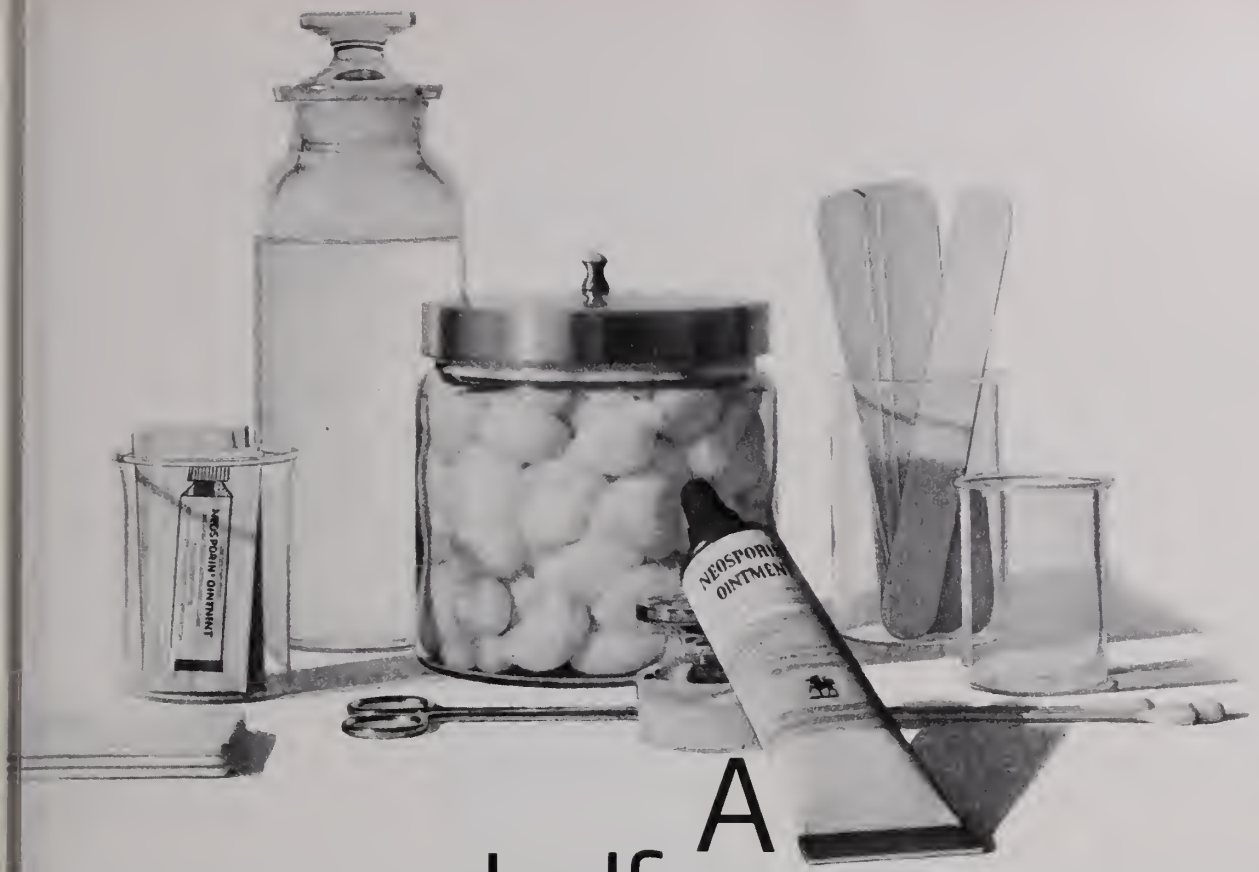
1975 Symposium on Diabetes Mellitus, February 22, 9 a.m. to 4:30 p.m. Contact: Mrs. Donna Fillmer, American Diabetes Association of Minnesota, W-414 Meadowbrook Building, 6490 Excelsior Blvd., Minneapolis 55426. (612) 927-4487.

Minnesota Radiological Society

Winter Meeting, February 1, 1975, Minnesota Club, St. Paul, Minnesota—8:00 P.M.

The First K. W. Stenstrom Memorial Lecture to be given by Leo G. Rigler, M.D., Professor and Chairman Emeritus, Department of Radiology, University of Minnesota and Professor of Radiology, Department of Radiological Sciences, University of California, Los Angeles.

"A Successful Academic Partnership: K. Wilhelm Stenstrom and the Department of Radiology of the University of Minnesota." Contact: Marvin Goldberg, M.D., Box 292, Mayo Memorial Health Sciences Center, Minneapolis. (612) 373-8650.



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TIONS: *Therapeutically,* used as an adjunct to appropriate systemic for topical infections, primary or secondary, due to susceptible organ- in: • infected burns, skin grafts, surgical incisions, otitis externa ry pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • second- nfected dermatoses (eczema, herpes, and seborrheic dermatitis) atic lesions, inflamed or suppurating as a result of bacterial infection. *hylactically,* the ointment may be used to prevent bacterial contamination , skin grafts, incisions, and other clean lesions. For abrasions, minor cuts unds accidentally incurred, its use may prevent the development of on and permit wound healing.

AINDICATIONS: Not for use in the eyes or external ear canal if the eardrum rated. This product is contraindicated in those individuals who have hypersensitivity to any of the components.

NG: Because of the potential hazard of nephrotoxicity and ototoxicity neomycin, care should be exercised when using this product in treating ve burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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Opinion & Dialogue

The Role of the Detail Man

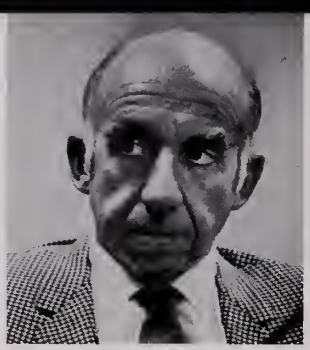


Dr. Willard Gobbell
Family Physician
Encino, California

"I may be prejudiced, but I a very much in favor of the detail m I meet. Most of them are knowled able about the drugs they promot and can be a great help in acquai ing me with new medication."

Family Physician's Perception

I think that most general practitioners in this area feel as I do about the detail man. Over the years I have gotten to know most the men who visit me regularly an they in turn have become aware o my particular interests and the na ture of my practice. They, there- fore, limit their discussion as muc as possible to the areas of interes to me. Since I usually see the sam representative again in future visits, it is in his best interest to supply me with the most honest, factual, as well as up-to-date information about his products.



Dr. Jeremiah Stamler
Chairman
Department of Community Health and Preventive Medicine, and Dingman Professor of Cardiology
Northwestern University Medical School

"In the total picture of deali with health problems in this coun there is a potential for detail men to play a meaningful role."

The Positive Influence

My contact with representa- tives and salesmen of the pharma ceutical industry is the type of co tact that people in a medical cent research people, and academic people have and that's in all likeli on a somewhat different level fro that of the practicing physician.

Let me touch on how I perso ally perceive the role of the sales representative. These men reach large numbers of health profes- sionals. Thus they could be—and at times actually are—disseminа- tors of useful information. They could consistently serve a real ed cational function in their ability t discuss their products.

At present they do distribute printed material, brochures and pamphlets—some of it scientific- ally sound and therefore truly use ful—as well as some excellent fil produced by the pharmaceutical industry. When they function in t

l: He a Source of Information?

Yes, with certain reservations. Te average sales representative hs a great fund of information aout the drug products he is re- sonsible for. He is usually able to aswer most questions fully and ielligently. He can also supply rprints of articles that contain a geat deal of information. Here, to, I exercise some caution. I usu- ay accept most of the statements ad opinions that I find in the cpers and studies which come fm the larger teaching facilities. goes without saying that a physi- can should also rely on other surces for his information on carmacology.

laining of Sales Representatives

Ideally, a candidate for the csition as a sales representative ca pharmaceutical company sould be a graduate pharmacist no has a questioning mind. I don't ink this is possible in every case, ed so it becomes the responsibility of the pharmaceutical company to train these individuals comprehensively. It is of very great importance that the detail man's knowledge of the product he represents be constantly reviewed as well as updated. This phase of the sales representative's education should be a major responsibility of the medical department of the pharmaceutical company.

I am certain that most of these companies take special care to give their detail men a great deal of information about the products they produce—information about indications, contraindications, side effects and precautions. Yet, although most of the detail men are well informed, some, unfortunately, are not. It might be helpful if sales representatives were reassessed every few years to determine whether or not they are able to fulfill their important function. Incidentally, I feel the same way about periodic assessments of everyone in the health care field, whether they be general practitioners, surgeons or salesmen.

Value of Sampling

I personally am in favor of limited sampling. I do not use sampling in order to perform clinical testing of a drug. I feel that drug testing should rightly be left to the pharmacology researcher and to the large teaching institutions where such testing can be done in a controlled environment.

I do not use samples as a "starter dose" for my patients. I do, however, find samples of drugs to be of value in that they permit me to see what the particular medication looks like. I get to see the various forms of the particular medication at first hand, and if it is in a liquid form I take the time to taste it. In that way I am able to give my patients more complete information about the particular medications that I prescribe for them.

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pacity they are indeed useful; rticularly in the fact that they sseminate broadly based educa- onal material and serve not just "pushers" of their drugs.

e Other Side of the Coin

Obviously, the pharmaceuti- l companies are not producing all is material as a labor of love— ey are in the business of selling oducts for profit. In this regard e ambitious and improperly moti- ted sales representative can ert a negative influence on the acticing physician, both by pre- nting a one-sided picture of his oduct, and by encouraging the actitioner to depend too heavily drugs for his total therapy. In ese ways, the salesman has often storted objective reality and ndermined his potential role as an ducator.

he Industry Responsibility

Since the detail man must be n information resource as well as representative of his particular harmaceutical company, he ould be carefully selected and thoroughly trained. That training, perforce, must be an ongoing one. There must be a continuing battle within and with the pharmaceutical industry for high quality not only in the selection and training of its sales representatives, but also in the development of all of its promotional and educational material.

The industry must be ready to accept constructive as well as corrective criticism from experts in the field and consumer spokesmen, and be willing to accept independent peer review. The better educated and prepared the salesman is, the more medically accurate his materials, the better off the pharmaceutical industry, health professionals and the public—*i.e.,* the patients—will be.

Physician Responsibility

The practicing physician is in constant need of up-dated information on therapeutics, including drugs. He should and does make use of drug information and answers to specific questions supplied by the pharmaceutical representative. However, that information must not be his main source of continuing education. The practitioner must keep up with what is current by making use of scientific journals, refresher courses, and information received at scientific meetings.

The practicing physician not only has the right, but has the responsibility to demand that the pharmaceutical company and its representatives supply a high level of valid and useful information. I feel certain that if such a high level is demanded by the physician as well as the public, this demand will be met by an alert and concerned pharmaceutical industry.

From my experience, my impression is that sectors of the pharmaceutical industry are indeed ethical. I challenge the industry as a whole to live up to that word in its finest sense.

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Rural Physician Associates

Rural Physician Associate Program Progress Report

May 15, 1974
Minnesota State Medical Association, Duluth, Minn.

THE UNPRECEDENTED medical education effort of the Rural Physician Associate Program is now beginning to take form in partial outcomes. Sponsored by the University of Minnesota Medical School and supported by state and federal funds; 23 students for 1971-72, 37 for 1972-73, and 26 for 1973-74. They have been diffusely scattered with practicing family physicians.

The aim of the program is to encourage the beginning senior medical student to choose a career of broad medical care in a rural area of the state. They have a choice while on the program of remaining in the rural community for nine to 12 months. They receive two quarters of academic credit and continue for nine months at the Medical School following completion of the program. On returning to Medical School, they "plug in on the weaknesses" they now recognize in their knowledge and skill-base. Ninety-five percent of the 1971-72 class are in rotating internships or family practice residencies, while 82% of their classmates not on the program have gone into similar internship-residency programs.

Positive spin-offs from the program include the following:

1. The majority of the communities on the program the first two years now have new broad-based physicians, ranging from one to five in number per community! A significant number of these new physicians have been trained outside the state!

2. The communities' practicing physician-teacher-preceptors have stated they desire to remain on the program because it has been one of the best post graduate medical education efforts available for them.

3. The students' critiques of the program reveal, generally, the experience has been one of the most significant medical school experiences up to this point in their educational career. It has been the most enjoyable and has made them more comfortable and confident in the care of the community population.

4. Other health and disease professionals (hospital administrators, nurses, technicians, therapists, social workers, public health nurses, executive directors of welfare, and others) have been intimately and enthusiastically involved in support, development, and maintenance of the program.

5. Other states and schools (North Dakota) are beginning to use the program for similar benefits.

6. The medical students have learned to extract valid data from patients and their families by seeing themselves, live, performing as family physicians on audiovisual tape. They have learned to integrate this data for creative problem solving by support from faculty who have expertise in marriage counseling and communications.

The Rural Physician Associate Program has partially fulfilled the aims and objectives to this date.

John E. Verby, M.D.*
Minneapolis, Minnesota

*Professor, Department of Family Practice and Community Health, University of Minnesota Medical School, Minneapolis.

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IMMEDIATE OPENINGS for Family Practitioner and Internist; community of 5000; 50 miles west of Minneapolis; 8 Doctors on 54 Bed Hospital Staff rotating night and weekend coverage. Salary negotiable; independent or associate practice. Contact Hospital Admin., David Larson, 705 W. 18th Street, Glencoe, MN 55336 or phone (612) 864-3121 collect.

WANTED—Internists and Family Practitioners to join congenial five man group in central Wisconsin. Completion of new office complex adjoining new modern hospital expected soon. Excellent starting salary with liberal time off for vacation, postgraduate studies, etc. Contact Clifford Starr, M.D., Riverwood Clinic, 1011 3rd Street South, Wisconsin Rapids, Wisconsin, (715) 423-1300 or Dean Nelson, Administrator, Riverview Hospital, 410 Dewey Street, Wisconsin Rapids, Wisconsin, (715) 423-6060.

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continued to page 88

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- Reasonable cost*



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AN IMPORTANT NOTE:
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CHOLOXIN® (sodium dextrothyroxine) Single-Tablet-A-Day Dosage Schedules

See prescribing information in package insert reproduced below.

	Starting Dosage	Increased Monthly by	Usual Maintenance	Maximal Recommende
Adult Hypercholesterolemic	1.0-2.0 mg.	1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac	0.5-1.0 mg.	1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as D-3,5,3′,5′-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

Special Article

Light Microscopy of Glomerular Disease

Applications of A Morphologic Diagnosis

ABE FOX, JR., M.D.*

Light microscopic anatomic pathology of renal glomerular diseases with emphasis on deriving an objective morphologic diagnosis and appropriate clinical differential diagnoses.

THE FOLLOWING IS A review of glomerular pathology as defined by light microscopy, using selected special staining techniques. Anatomic definition of these abnormalities is stressed to obtain a basic anatomic reference point, a *morphologic diagnosis.*

The values of a morphologic diagnosis are real. Too often an attempt is made to apply a specific clinical term or etiologic diagnosis to histologic abnormalities. Though such specific abnormalities exist, they are exceptions, not the rule. One may recognize a morphologic abnormality which is precisely definable, derive a differential diagnosis, and search from this point for more specific pathologic or clinical features. Further, morphology alone may discretely measure prognosis, regardless of etiology. Objective morphologic and clinical interpretations are made independently. Then the two are considered together in order to best assess the patient's disease.

Why Light Microscopy?

Ideally, either renal biopsy tissue is split or multiple samples are obtained for light microscopy, immunofluorescence, and electron microscopy. Unfortunately it is impractical and frequently impossible to perform all three in most institutions.

When light microscopy and immunofluorescence studies are done routinely, electron microscopy usually provides little additional practical diagnostic information. Most glomerular lesions commonly illustrated with fluorescence or electron microscopy may be identified with light microscopy when selected special staining techniques are applied.†

Special stains offer an excellent retrospective study tool. Formalin fixed, paraffin embedded archive tissue is usually unsatisfactory for electron microscopy or fluorescence studies.

Some stains, in particular periodic acid methenamine silver, provide an excellent "bridge" between electron microscopy and light microscopy. Many normal anatomic structures and abnormalities of the renal glomerulus that are inconspicuous with routine stains are readily identified.

Overall, light microscopy alone usually answers the cogent clinical questions for which the renal biopsy for diagnosis is performed (i.e. *what is the disease process?, what is the differential diagnosis?;* and *what is the prognosis?*)

Anatomy of the Glomerulus

The Renal Glomerulus is a complex of multiple groups of anastomosing capillaries which originate from the afferent (precapillary) arteriole and recombine to form the efferent (postcapillary) arteriole. The groups of capillaries are referred to as *Lobules;* the composite is called the *Glomerular Tuft.*

The Glomerular *Mesangium* accompanies the arterioles at the vascular pole and extends into the glomerular tuft to occupy the central region of the lobules. The centrolobular intercapillary region is also frequently referred to as the *stalk* or *axial* region.

The Glomerulus is bound externally by the *Urinary Space* (U.S.) which receives the glomerular filtrate. The urinary space is limited by *Bowman's Capsule* (B.C.). The basement membrane of Bowman's capsule is continuous with that of the Proximal Convoluted Tubule (P.C.T.). The renal glomerulus and associated structures en-

*Department of Pathology, Methodist Hospital, St. Louis Park, Minnesota.

†For Methods, see "Technical Notes."

closed by Bowman's Capsule comprise the *Renal Corpuscle.*

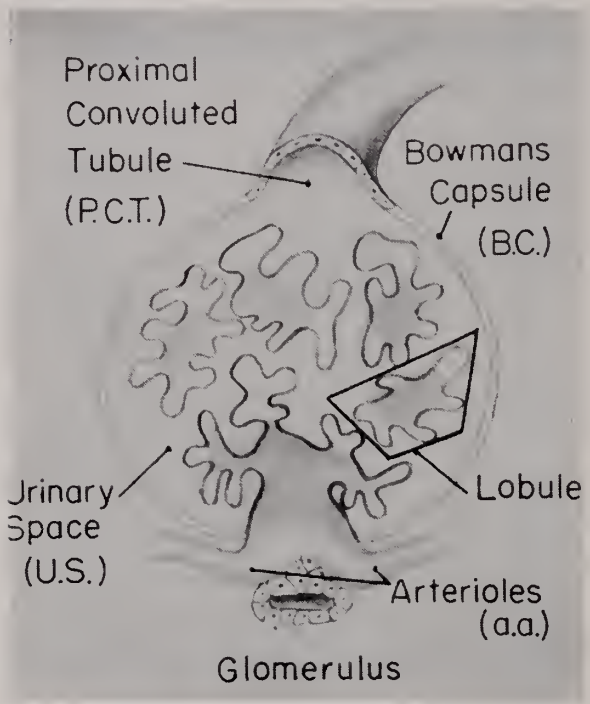


Fig. 1—Diagram of cross sectional anatomy of the renal glomerulus and related structures. The glomerular capillaries ascend into the renal corpuscle from the vascular pole (see Arterioles; a.a.) The intercapillary mesangium is shaded. The glomerular tuft is segmented into multiple lobules peripherally. The extracapillary urinary space is limited by Bowman's Capsule which is continuous with the Proximal Convoluted Tubule.

Glomerular Lobule

The *Capillary Basement Membrane* (C.B.M.) is continuous at the perimeter of the glomerular lobule. The glomerular capillaries are fully enclosed by the basement membrane. The mesangium is interposed between the capillaries in the central stalk region. The capillary basement membrane is contiguous with the mesangium in the centrolobular regions. Therefore, abnormalities of the capillary basement membrane are best separated from abnormalities of the mesangium by examination of the *peripheral* capillary basement membrane.

Visceral Epithelial Cells (v.Ep.) line the extracapillary surface of the capillary basement membrane. Similar *Parietal Epithelial Cells* (p.Ep.) extend from the vascular pole of the glomerulus along Bowman's Capsule to the proximal convoluted tubule. These epithelial cells are large with a readily apparent quantity of cytoplasm and have elliptical nuclei with dispersed nuclear chromatin. By electron microscopy, numerous small extensions of the visceral epithelial cells abut the capillary basement membrane. The extensions are descriptively termed "foot-processes" and the cells are therefore frequently referred to as "podocytes".

Endothelial Cells (En.) border the intraluminal side of the capillary basement membrane. Normally, one to three are seen per lobule in 1-3 u sections. The endothelial cytoplasm is attenuated and not readily identified with light microscopy in the normal glomerulus. The nuclei are smaller than the epithelial nuclei and the nuclear chromatin is more dense.

At the center of the lobule, the intercapillary material is referred to as the *Mesangial Matrix* (M.M.) The mesangial matrix is coursed by multiple irregular filamentous structures (Mesangial Fibrils) with staining characteristics similar to the capillary basement membrane.

Mesangial Cells (M.) are by definition the cells within the intercapillary mesangial regions. Mesangial cells are slightly smaller than endothelial cells and have oval nuclei. Their cytoplasmic membranes are indistinct and fuse with the mesangial fibrils. Cytologic characteristics of endothelial and mesangial cells are similar. Mesangial cells between isolated capillaries may also be confused with visceral epithelial cells. For

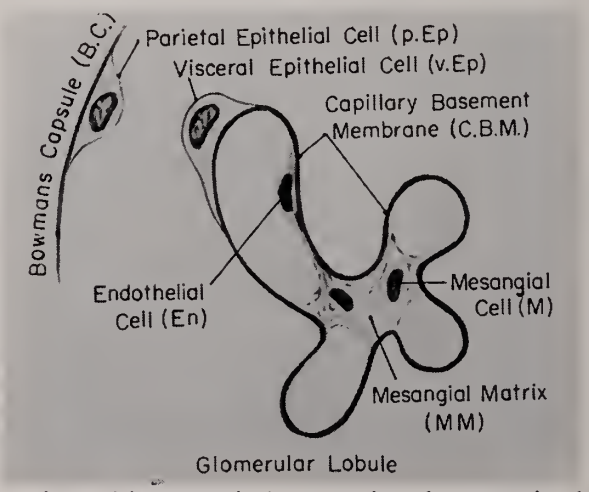


Fig. 2—Diagrammatic demonstration of cross sectional anatomy of the glomerular lobule and a small portion of Bowman's capsule. The capillary basement membrane is continuous about the group of capillaries. It does not completely encircle the individual capillaries. The capillaries are bordered in the stalk or intercapillary region by the mesangium. The extracapillary epithelial and intraluminal endothelial cells are defined by reference to the peripheral capillary basement membrane. Mesangial cells are identified by their centrolobular or intercapillary position or by demonstration of the matrix fibrils of the associated mesangium.

these reasons identification of the cell type demands definition of the centrolobular anatomy or demonstration of the fibrillar matrix of the mesangium. Similar endothelial and epithelial cells are best separated by reference to their position with respect to the peripheral capillary basement membrane.

Applied Anatomy

In disease, the glomerular alteration is most commonly characterized by predominantly cellular, membranous, or mesangial changes. Proper identity of the abnormality anatomically is an integral part of the morphologic diagnosis. The constant reference points are the glomerular tuft and lobule, capillary basement membrane and the intercapillary glomerular mesangium.

Proliferative Processes

Proliferative disease processes are abnormalities of the glomerulus in which there is an increase in the number of one or more of the cellular components of the glomerulus. The proliferating cells frequently appear cytologically quite different from normal and for this reason, the cell type or types involved are best defined by anatomic reference to the capillary basement membranes and the mesangium.

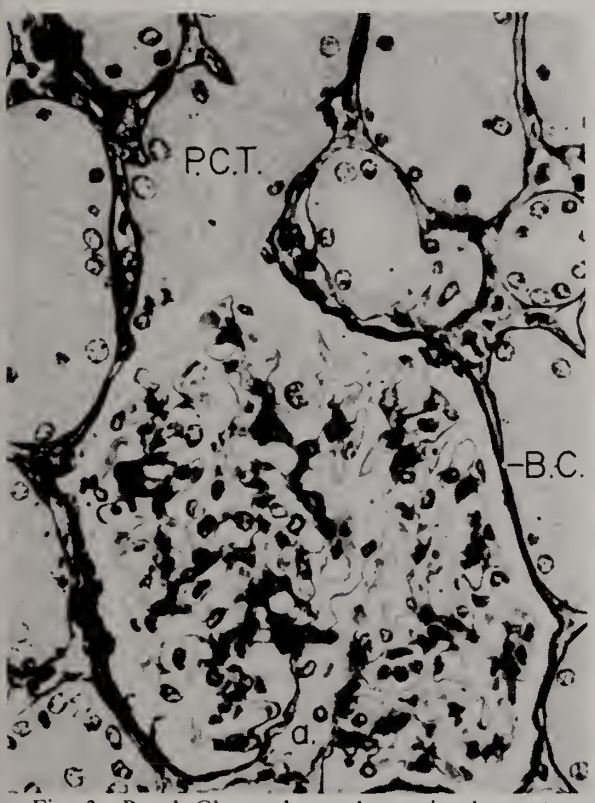


Fig. 3—Renal Glomerulus and associated structures (Renal Corpuscule). A cross-section of one of the glomerular arterioles (a) is included at the vascular pole. Bowman's capsule (B.C.) marks the external boundary of the urinary space which is continuous with the proximal convoluted tubule (P.C.T.) receiving the glomerular infiltrate. The capillaries arise from the precapillary arteriole and branch into multiple groups or lobules of anastomosing capillaries. The composite of all the capillary lobules and the associated mesangium comprise the renal glomerulus.

Epithelial Proliferation

An increase in the number of cells external to the peripheral capillary basement membrane within the urinary space is an *Epithelial Proliferative* process. The proliferation is, by definition, extracapillary. The changes may be minimal; the most notable abnormality often is an increase in cell size ("podocytic swelling"), with minimal increase in the number of cells. In other instances, the epithelial proliferation results in the formation of syncytial groups of the proliferating cells over the glomerular tufts, referred to as "crescents". In instances of extensive epithelial proliferation, hypercellular crescents appear to obliterate the urinary space.

Endocapillary Proliferation

Endocapillary Proliferation is an increase in the number of cells within the capillary lumina. The

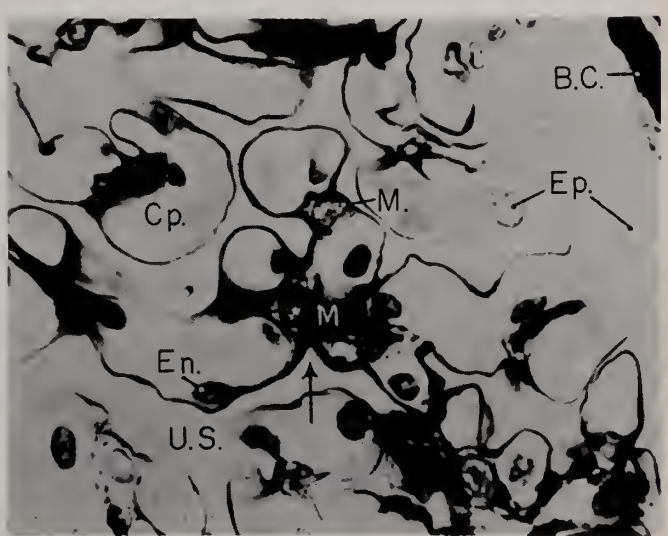


Fig. 4—Glomerular lobule. The centrolubular region is identified by the dark staining mesangium in the center of the photograph. (See arrow) Extracapillary epithelial cells (Ep.) and intraluminal endothelial (En.) cells are identified by reference to the peripheral capillary basement membrane. A single mesangial cell is apparent between one capillary of the lobule and another isolated capillary. (see M above). The capillary basement membrane is continuous at the periphery of the lobule; centrolobular portions of the capillaries are bordered by the mesangium. (Cp: capillary; U.S.: urinary space) (Periodic acid methenamine silver X 750).

cells are internal to the peripheral capillary basement membrane, exclusive of the centrolobular mesangial cells. Endothelial cell proliferation is frequently accompanied by swelling of the endothelial nuclei. The nuclear chromatin is more dispersed and the cytoplasm is more evident than normal. In this instance, the cells are similar in appearance to epithelial cells.

When the endothelial proliferative process is extensive, the capillary lumina may all be virtually occluded and the hypercellular glomerular tuft may appear to fill the renal corpuscular space and even distend it. In some florid intracapillary proliferative states, probably involving mononuclear blood cells, mesangial, and endothelial cells, it may be virtually impossible to individually define all intracapillary cell types. In these instances identification of the predominant cell type is usually of no practical significance and endocapillary proliferation is the most practical descriptive term.

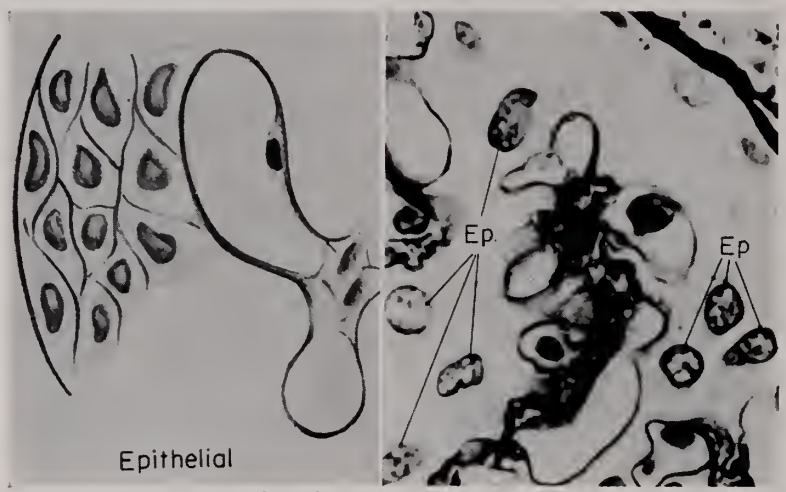


Fig. 5—Epithelial Proliferation. *(Left)*, diagram of epithelial proliferation defined by the presence of an increased number of cells external to the peripheral capillary basement membrane. *(Right)*, the epithelial cells are increased in number and swollen. They are identified as epithelial on the basis of their cytologic characteristics and extracapillary position within the urinary space. (Periodic acid methenamine silver X 960).



Fig. 6—Endothelial Proliferation. *(Left)*, diagram of endocapillary-endothelial proliferation. There is an increase in the number of cells internal to the peripheral capillary basement membrane exclusive of cells in the mesangial region. *(Right)* marked increase in endocapillary cellularity which is predominantly endothelial (En.) There is virtual obliteration of the endocapillary spaces by cells and amorphous material. The endothelial cells are swollen and their nuclei are more vesicular than normal. Despite the severity of the process, identification of the endocapillary location of the pathology is readily made by reference to the capillary basement membranes. (Periodic acid methenamine silver X 750).

Mesangial Proliferation

Mesangial Cellular Proliferation is identified by anatomic reference to the intercapillary or centrolobular portion of the glomerular lobule. Typically, the lobular mesangium appears expanded and there are increased numbers of cells within the centrolobular region. Frequently, this results in accentuation of the lobular architecture of the glomerulus. The expanded mesangial region and the mesangial cells may encroach on the centrolobular portions of the capillaries.

Applied Anatomy: "Membranous" Processes

(Non-Cellular Lesions Related to the Peripheral Capillary Basement Membranes)

As with proliferative processes, abnormalities of the capillary basement membranes are similarly defined by reference to the anatomy of the glomerular lobule. Of necessity, peripheral capil-

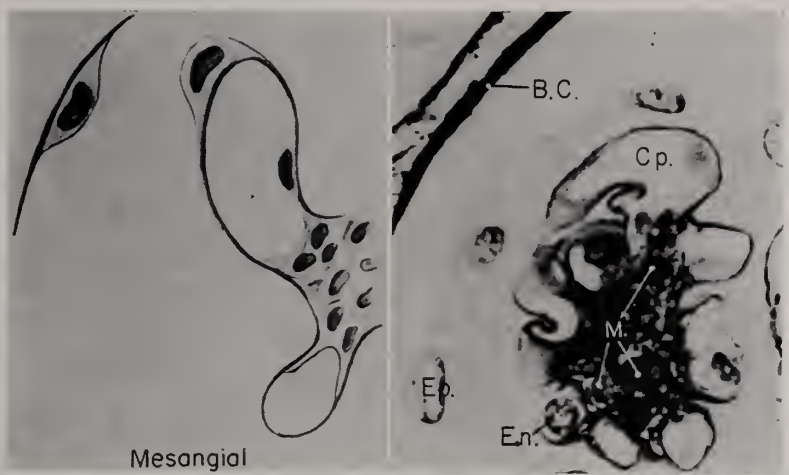


Fig. 7—Mesangial Cellular Proliferation. *(Left),* diagram of mesangial cellular proliferation defined by increased numbers of cells within the expanded mesangial region. *(Right),* the peripheral capillaries are more widely separated than normal. Within the expanded mesangial region, there are increased numbers of mesangial cells. In addition, there is epithelial cellular swelling in the region of the same lobule. (Periodic acid methenamine silver X 960).

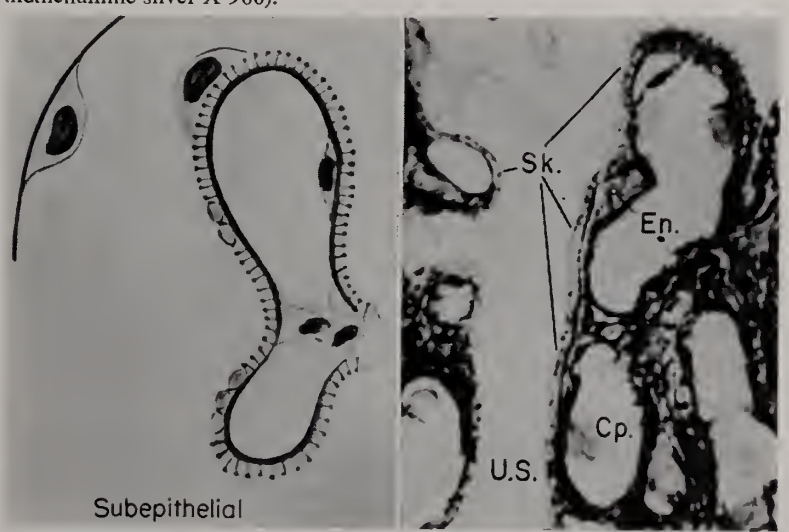


Fig. 8—Diffuse Subepithelial Deposit Membranous Lesion. *(Left),* diagrammatic representation of the process as identified with methenamine silver preparations. Numerous spikes project into the urinary space from the epimembranous or subepithelial aspect of the peripheral capillary basement membrane. *(Right),* Diffuse subepithelial membranous lesion with numerous spikes (Sk.) extending into the urinary space. Note the uniformity of involvement of all the peripheral capillary basement membranes included in the plane of the photograph. (Gomori methenamine silver-Helly's fixative X 1200).

lary basement membranes are examined. This precludes the difficulties of differentiating membranous abnormalites from abnormalities of the mesangium.

The membranous lesions are a result of aggregation of material within or on one side of the capillary basement membrane. The aggregates of material are referred to as deposits. They are, by inference, predominantly protein and, in part, antibody globulin. Other proteins may be present as well (complement components, derivatives of fibrinogen, etc.). The capillary basement membranes per se may or may not be thickened.

Subepithelial Deposits

Some membranous processes are the result of the presence of deposits on the extracapillary surface of the capillary basement membrane. The deposits are, of necessity, anatomically beneath the visceral epithelial cells. Therefore the morphologic description of the process in *Subepithelial; Extracapillary* or *Epimembranous* are equally descriptive. There are three basic morphologic types of subepithelial deposit processes. These are the deposit-spike lesion, the subepithelial "Hump", and epimembranous fibrilar masses.

Diffuse Subepithelial Deposit-Spike Lesion

The diffuse *Subepithelial Deposit-Spike Lesion* is the result of the presence of small deposits uniformly present over the extracapillary surface of all the capillary basement membranes. The capillary basement membranes of all the capillaries appear thickened at low magnification.

With methenamine silver staining techniques, numerous regularly spaced nail shaped projections or "spikes" project into the urinary space from the extracapillary surface of the capillary basement membranes. When properly demonstrated, this spike lesion is the most distinctive.

Subepithelial "Hump" Lesion

This lesion consists of irregularly-sized and usually sporadically spaced obtuse deposits on the extracapillary surface of the capillary basement membranes. The superficial surface of the deposit is convex resulting in a configuration reminiscent of a camel's hump.

The "hump" stains red or red-orange with trichrome preparations. With methenamine silver stains, they are colorless or grey-brown.

Epimembranous (Subepithelial) Fibrillar Deposits

Masses of subepithelial fibrillar appearing silver positive material are common in glomerular amyloidosis and apparently unique for that process. These fibrillar or "hairy" appearing structures project vertically from the capillary basement membrane into the urinary space. As a result the capillaries appear bearded. Less frequently, these

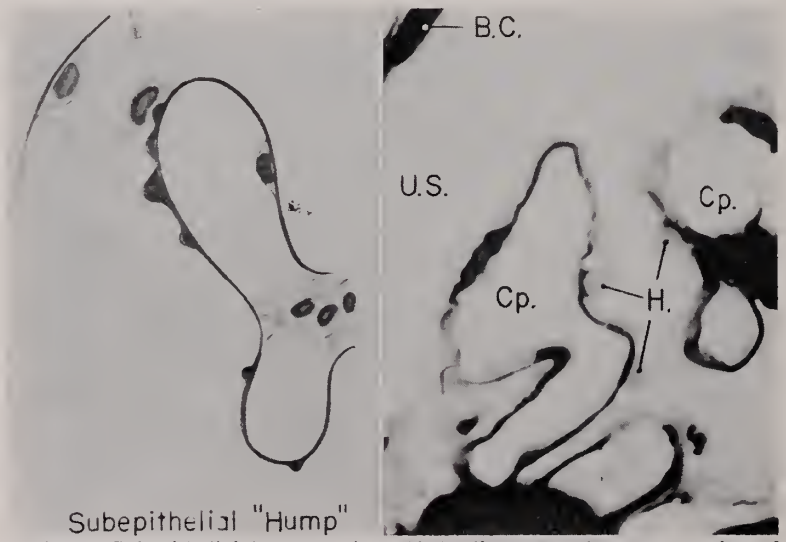


Fig. 9—Subepithelial Hump Lesion. *(Left)* diagrammatic representation of the "Hump" lesion. Multiple obtuse deposits of varying size are present on the extracapillary surface of the periphery capillary basement membranes. *(Right)* the typical obtuse configuration of the subepithelial "Hump" (H.) is demonstrated in this example. Multiple lesions of varying size are present. Note the epimembranous or subepithelial situation of the Humps on the peripheral capillary basement membranes. (Periodic acid methenamine silver X 1500).

same structures appear to project into the capillary lumina. Mesangial amyloid, usually prevalent, is silver positive but not fibrillar appearing by light microscopy.

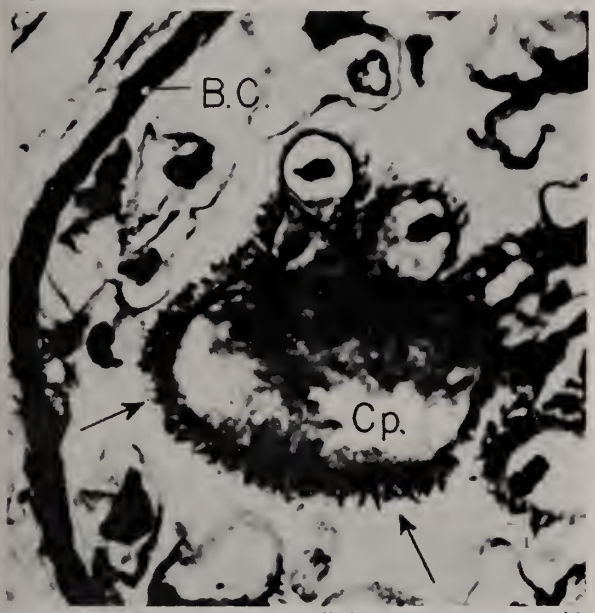


Fig. 10—Epimembranous Fibrillar Masses, Amyloid. Numerous masses of fibrillar appearing material are present on the epimembranous surface of the capillary basement membrane. As a result the capillaries appear "bearded" (Periodic acid methenamine silver X 1500).

Subendothelial Deposits

Deposits may be distributed on the endocapillary surface of the basement membrane, immediately beneath the endothelial cells. These *Subendothelial Deposits* are variable in size and resolution of small deposits demands thin sections. A spectrum of larger crescentic, serrated, or segmented appearing agglomerates may be present.

With the trichrome stains, these lesions are usually red-orange; older lesions may stain blue. The methenamine silver methods stain these deposits grey or brown. They frequently appear to separate a thin foil of the intracapillary portion of the capillary basement membrane.

Intramembranous Deposits

Intramembranous Deposits result in an apparent near perfect splitting of the capillary basement membrane such that it is impossible to clearly define orientation of the deposits to the capillary basement membrane as previously discussed (i.e., subendothelial or subepithelial). The intramembranous space may appear to be void of material or contain irregular serpentine deposits. Frequently the result is a symmetrical double membrane appearance or a "railroad-track" configuration of the capillary basement membrane. The double membrane may look twisted or braided.

The majority of intramembranous lesions are contiguous with mesangial lesions. Rarely argentophillic intramembranous deposit processes involve the basement membranes of Bowman's capsule, the renal tubules, and renal vessels, as well as the glomerular capillaries.

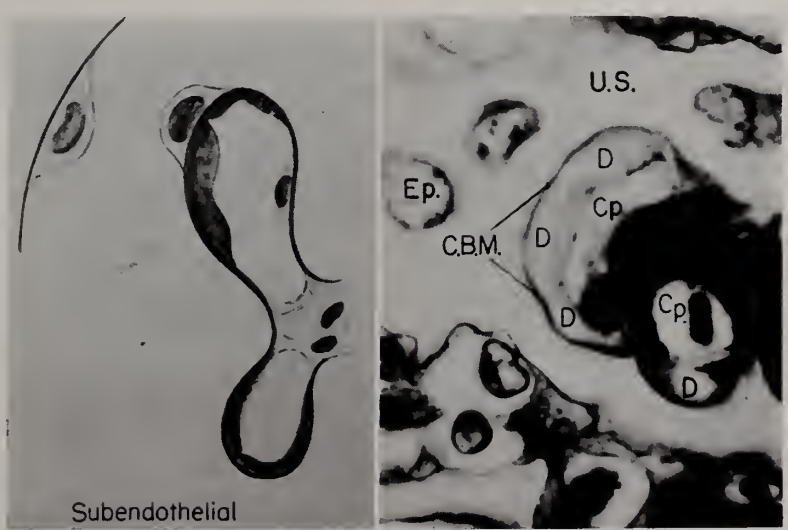


Fig. 11—Subendothelial Deposits. *(Left)* diagrammatic representation of subendothelial deposits. The deposits border the intraluminal aspects of the peripheral capillary basement membrane. *(Right),* subendothelial deposits (D.) as demonstrated by the Periodic acid methenamine silver stain. The material is deposited on the intraluminal aspect of the peripheral capillary basement membrane (C.B.M.). (Periodic acid methenamine silver X 1500).



Fig. 12—Intramembranous deposits. *(Left),* diagrammatic representation of morphology of intramembranous deposits. The capillary basement membrane appears split by the deposits. As a result there appears to be replication of the basement membrane or a double membrane or so-called "dual track." *(Right)* intramembranous deposits as demonstrated with the Periodic acid methenamine stain. In this example, the deposits are argentophilic. The deposits (D) appear neither subendothelial or subepithelial but intramembranous. There is also an increase in the number of mesangial cells in the lobule. (X 1200).

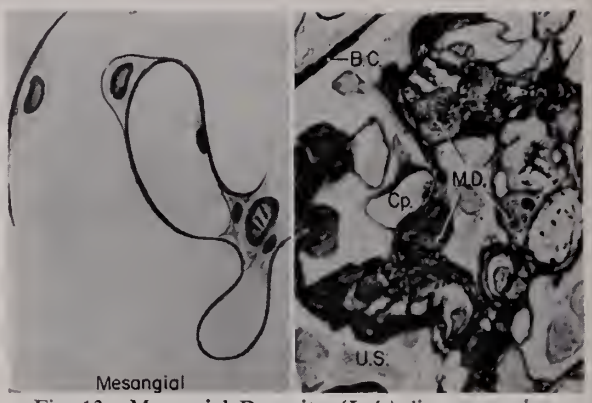


Fig. 13—Mesangial Deposits. *(Left)* diagrammatic representation of a mesangial deposit within the intercapillary region. The deposit is within the mesangial region, separate from the capillaries. *(Right)* multiple globular deposits (M.D.) are present within these intercapillary mesangial regions. The mesangial areas appear broadened and the mesangial fibrillar material appears dispersed by the deposits. The majority of the peripheral capillary basement membranes appear normal. (Periodic acid methenamine silver X 960).

Applied Anatomy: Non-Cellular Mesangial Lesions

Non-cellular lesions of the glomerular mesangium are common in glomerular disease. The two most commonly encountered are mesangial deposits and "sclerosis". Increased mesangial cellularity may accompany these processes.

Mesangial Deposits

Mesangial deposits have the same staining characteristics of deposits related to the capillary basement membrane but are identified within the anatomic intercapillary or centrolobular regions. The deposits vary considerably in size. They may be small and granular or large and globular.

The mesangial region usually appears broadened or expanded by the mesangial deposits, but may be free of cellular proliferation. The mesangial fibrils usually appear dispersed by the deposit material. Mesangial deposits frequently extend into the capillary loops and appear to have split the capillary basement membrane and therefore appear intramembranous. When this occurs, identification of the mesangial fibrillar material in association with the deposits is helpful in identifying the mesangial origin of the process.

Mesangial Sclerosis

Mesangial Sclerosis is an apparent replication of the intercapillary fibrillar material. The mesangial region is expanded and increased numbers of broad fibrils are present in the enlarged intercapillary space. The sclerotic change may extend into the centrolobular portions of capillaries and along the capillary basement membranes. Mesangial cellular proliferation and mesangial deposits may accompany the sclerosis.

In some instances sclerosis of mesangium is associated with expansion of this region by large spheroid amorphous masses of material with staining characteristics of collagen *(Nodular*

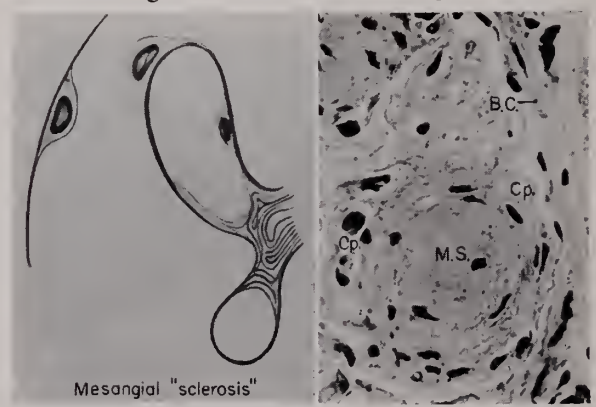


Fig. 14—Mesangial sclerosis. *(Left),* diagrammatic representation of mesangial sclerosis. There is expansion of the region with an increase in the numbers of mesangial fibrils, morphologically suggesting replication of the fibrillar material. The change extends superficially into the capillaries. *(Right)* mesangial sclerosis (M.S.) associated with a discrete nodule in the centrolobular region of a glomerular lobule. The peripheral capillary lumina appear patent but relatively diminished in size by the process. There are numerous slit-like spaces between the mesangial fibrils which are concentrically arranged about the periphery of the nodule. (Masson trichrome X 600).

Mesangial Sclerosis). The mesangial fibrillar material is usually scattered throughout the lesion and present in concentric rings about the periphery of the nodule.

Descriptive Morphologic Classification of Glomerular Disease

In reviewing renal pathology, it is necessary to examine all parts of the nephron. The glomeruli, tubules, vessels, and interstitium should be examined individually and together. The glomerular changes may appear dominant but may in fact be secondary to primary disease of the other structures. In turn abnormalities of the vessels, tubules, and interstitium may appear dominant and be secondary to a primary glomerular disease. Regardless of the primary insult, the morphology of the glomerular lesion may be described as a *glomerulopathy.*

The classification used in defining the glomerular abnormalities morphologically is of necessity descriptive. The distribution of the disease process is examined and described first. The first questions to be answered are how many of the glomeruli are involved and what fraction of the individual glomerulus is abnormal?

Different preferences exist with regard to terminology, but the basic descriptive morphologic analysis applied is common to all terminologies. In this text when the abnormality involves all of or most of the glomeruli, the process is classified *generalized. Focal* abnormalities involve a minority or only a few of the glomeruli. If the entire glomerular tuft is affected, the process is *diffuse.* If parts of lobules or isolated lobules of the glomerular tufts are involved but the majority of the lobules are spared, the process is *segmental.* This classification is that suggested by Allen. One may briefly review this terminology comparing it to the synonomous terms of an excellent descriptive alternative, that of McMannus, as follows:

Generalized: Omniglomerular: Majority of or all glomeruli involved

Focal: Pauciglomerular: Minority of or few glomeruli involved

Diffuse: Totiglomerular: Majority of or all lobules involved

Segmental: Partiglomerular: Minority of or parts of lobules involved.

Generalized processes usually involve more than 80% of the glomeruli; focal lesions frequently involve less than 20% of the glomerular tufts. Processes of intermediate extent of involvement may be difficult to properly classify, particularly in renal biopsies with too few glomeruli.* This is not usually a major problem when an adequate number of glomeruli are present in the biopsy and further suggestion as to the number of glomeruli involved is frequently indicated by the extent of

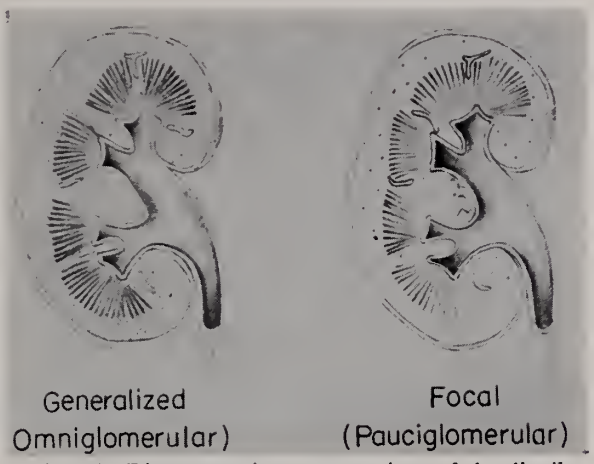


Fig. 15—Diagrammatic representations of the distribution of glomerular disease with respect to the number of glomeruli involved. Generalized or omniglomerular processes *(left)* involve a majority or most of the glomeruli, usually in excess of 80%. In contrast, focal or pauciglomerular lesions *(right)* involve a minority of the glomeruli, frequently less than 20%.

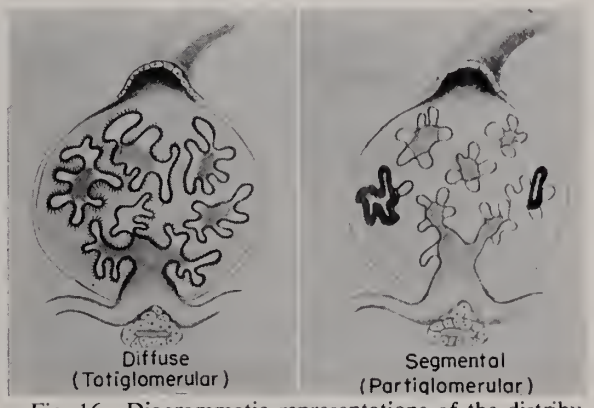


Fig. 16—Diagrammatic representations of the distributions of glomerular abnormalities within individual glomeruli. An example of diffuse or totiglomerular membranous alteration is illustrated on the *left.* Tiny spikes are present over the extracapillary surface of *all* the glomerular capillaries. *(Right),* segmental (partiglomerular) abnormalities involve either isolated parts of the glomerulus or occasional lobules within the glomerulus. The remaining lobules are normal. This illustration is representative of a membranous lesion which is segmental in distribution. The majority of the capillary basement membranes are normal.

*When fewer than six glomeruli are included in a biopsy sample it is prudent to reserve judgment as to the number of glomeruli involved unless the process is well defined in that small group. Biopsies including more glomeruli may also be misleading, subject to the random anatomic site of the biopsy sample.

involvement of the individual glomeruli. Diffuse glomerular lesions are most commonly generalized; segmental glomerular lesions are most often focal. There are, however, several exceptions to this rule (i.e., generalized-segmental and focal-diffuse processes).

Morphologic Diagnosis and the Clinical Differential Diagnosis

The goal of the microscopist is to establish a precise morphologic diagnosis and from this offer a differential of the clinical diseases which result in the histopathology identified. In most instances the differential diagnosis is relatively finite, unfortunately in some almost unlimited. In a few instances the morphology is diagnostic of a specific disease process.

The following Tables (1-A thru E) are offered as a *worklist* of differential diagnosis, *not* an ultimate complete tabulation, derived from identified cellular and noncellular lesions according to their distribution. These differentials may be incomplete but include likely possibilities.

Most glomerular diseases manifest multiple histologic abnormalities, some more specific than others. When one lesion is identified, search for associated lesions is therefore helpful in narrowing the differential diagnosis. Clinical diseases are itemized in Table 2 to include combinations of common light microscopic lesions. Tables 1-A,B,C,D, and E are referenced to Table 2 by Key number (e.g. k-1, k-2, etc.)

Proliferative Glomerulopathies (Table 1-A)

Endocapillary Proliferation

Generalized diffuse endocapillary proliferation is the cellular histologic hallmark of an acute immune complex process involving the renal glomerulus (i.e. Acute Proliferative Glomerulonephritis). Diffuse subepithelial humps are usually present early. As the process subsides, mesangial hypercellularity and mesangial deposits persist, frequently for many months.

Clinical Differential Diagnosis:

Post bacterial infection (e.g. post streptococcal)

Post viral infection (e.g. post varicella)

Serum sickness

Occasionally, generalized and diffuse endocapil-

TABLE I-A
Glomerular Lesions-Distribution in disease
Proliferative
Clinical Differential Diagnosis Worklist

	Generalized		Focal	
	diffuse	segmental	diffuse	segmental
ENDO	Acute Prolif. G.N. (k-1) Florid Acute Prolif. G.N, (k-3) with intracapillary thrombi	Lupus Nephritis, Glomerulonephritis type (k-19)	Persistent changes post Acute Prolif. G.N. (k-3)	Anaphylactoid Purpura (k-6) Lupus Nephritis, glomerulitis type (k-18)
	Var. Endotheliosis Eclampsia (k-17)	(Endothelial swelling) T.T.P., D.I.C., H.U.S. (k-23) Necrotizing glomerulitis (k-21, 22)	Malignant Hypertension Progressive Systemic Sclerosis (P.S.S.) (k-24)	Persistent Acute Prolif. G.N. (k-2)
	Acute Prolif. G.N. (k-1) Persistent Acute (k-2) Prolif. G.N.	Lupus Nephritis Glomerulonephritis type (k-19) Anaphylactoid Purpura (k-6)	Persistent Acute Prolif. G.N. (k-3) "Latent" Chronic G.N. (k-8)	Recurrent Hematuria, (k-5) glomerulitis syndrome (Berger's) Bacteremia, Endocarditis. Hepatitis B, glomerulitis Hypersensitivity Angiitis, Glomerulitis (k-22)
MES	Chronic Mesangio-capillary (hypocomplementemic) chronic Lobular G.N. (k-9) Renal "Dense Deposit Disease" Membranous Nephropathy (K-10) Chronic G.N. (k-8)	Chronic G.N.; (nonspec.) (k-8) Necrotizing Angiitis Glomerulitis (k-21, k-22)	Lipoid Nephrosis (k-13)	Rapidly Progressive G.N. (k-4) Goodpasture's syndrome (k-25) Polyarteritis Nodosa (k-21) Wegener's Granulomatosis Chronic G.N. (non spec.) (k-8)
EPI	Hypercellular crescents Rapidly Progressive G.N. (k-4) Goodpasture's Syndrome (k-25) Wegener's Granulomatosis (k-21) Anaphylactoid Purpura (k-7) (malignant form)		Wegener's Granulomatosis (k-21) Polyarteritis Nodosa (k-21) Hypersensitivity Angiitis (k-22) Anaphylactoid Purpura (k-6)	
	Fibrous Crescents Chronic G.N. (non spec.) (k-8)		Chronic G.N. (non spec.) (k-8) Healed Acute Necrotizing G.N. Healed Acute Prolif. G.N. (k-2)	
	Epithelial Swelling (Podocytic Swelling) Lipoid Nephrosis (k-13) Proteinuria (non spec.)		NonGlomerular Processes non-specific—proteinuria, hematuria, tuft necrosis	

TABLE 2
Glomerular Disease Key; Summary of Frequent Light Microscopic Glomerular Lesions

k-1	Acute Proliferative Glomerulonephritis	
	Generalized-diffuse	endocapillary proliferation
		epimembranous humps (variable)
		mesangial proliferation (variable)
		exudation (variable)
	e.g. Post Streptococcal, Post Varicella	
	Early	
	Generalized-diffuse	endocapillary proliferation
		epimembranous humps (acute immune complex process)
		exudation (variable)
		mesangial proliferation
k-2	Late (Persistent)	
	Focal	mesangial proliferation
		mesangial deposits
		mesangial sclerosis (variable)
k-3	Florid (Fulminant) Acute Proliferative Glomerulonephritis	
	Generalized-diffuse	endocapillary proliferation
		fibrin thrombi
		tuft necrosis
		epimembranous humps (variable)
		exudation
k-4	Rapidly Progressive Glomerulonephritis (Subacute-Malignant)	
	Generalized-segmental	epithelial proliferation (hypercellular crescents)
		tuft necrosis
		fibrin exudation urinary space
		mesangial proliferation (variable)
		endocapillary proliferation (variable)
k-5	Benign Recurrent Hematuria—Glomerulitis Syndrome—Berger's IGG-IGA Mesangial Lesion	
	Focal	mesangial deposits
		mesangial proliferation
		endothelial proliferation (variable)
k-6	Anaphylactoid Purpura-Glomerulitis	
	Focal-segmental	mesangial deposits
		mesangial proliferation
		tuft necrosis (variable)
		endothelial proliferation (variable)
k-7	"Malignant" Form (Rapidly-Progressive)	
	Generalized-segmental	epithelial proliferation (hypercellular crescents)
		tuft necrosis
		fibrin exudation urinary space
		mesangial proliferation (variable)
		endocapillary proliferation (variable)
k-8	Chronic Glomerulonephritis	
	"Latent" Chronic Glomerulonephritis*	
	Focal	endocapillary proliferation (variable)
		mesangial proliferation (variable)
		mesangial sclerosis (variable)
	Chronic Proliferative Glomerulonephritis (Chronic Glomerulonephritis—Nonspecific)	
	Generalized-diffuse	mesangial proliferation
		mesangial sclerosis (non-nodular)
		epithelial proliferation (fibrocellular or fibrous crescents)
	Focal-segmental	intramembranous deposits (variable)
		subendothelial deposits (variable)

*Clinical term . . . diagnosis may only be appropos in retrospect; similar abnormalities common with Resolving Acute Glomerulonephritis

(Continued to next page)

TABLE 2 (Continued)

		epimembranous deposits (variable) mesangial deposits (variable)
	Chronic Glomerulonephritis with Mesangial Deposits Only	
	Generalized-diffuse	mesangial deposits
	Chronic Sclerosing* Glomerulonephritis—"Focal Sclerosis" Syndrome	
	Generalized-diffuse	mesangial sclerosis (non-nodular)
	Focal	mesangial proliferation (variable) juxtamedullary global glomerular sclerosis "podocytosis" (variable)
k-9	Chronic Mesangio-Capillary and Lobular Glomerulonephritis "Hypocomplementemic-Membranoproliferative"	
	Generalized-diffuse	intramembranous deposits (non argyrophillic) mesangial proliferation
	Focal	nodular mesangial sclerosis
	"Lobular"—Late Stage Chronic Mesangio-Capillary Disease	
	Generalized-diffuse	nodular mesangial sclerosis intramembranous deposits (non argyrophillic) mesangial proliferation
k-10	Renal Membranous Nephropathy ("Dense Deposit Disease") Berger	
	Generalized RENAL†	argyrophillic intramembranous deposits mesangial proliferation endocapillary proliferation (variable)
k-11	Diabetic Glomerulosclerosis	
	Nodular	nodular mesangial sclerosis
	Focal-segmental	mesangial proliferation capillary basement membrane thickening (intramembranous-argyrophillic)
	Diffuse	
	Generalized-diffuse	mesangial sclerosis (non-nodular)
	Focal	mesangial proliferation capillary basement membrane thickening nodular mesangial sclerosis ("mixed" lesion)
k-12	Idiopathic Membranous Glomerulonephritis (Membranous Glomerulopathy)	
	Generalized-diffuse	epimembranous spikes (chronic immune complex process) granular epimembranous deposits epimembranous humps (variable) mesangial sclerosis (variable)
k-13	Lipoid Nephrosis (Nil Lesion-Nephrosis)	
	Generalized-diffuse	epithelial swelling ("podocytic swelling")
	Focal	mesangial sclerosis (juxta-medullary, non-nodular) juxtamedullary global sclerosis (see k-8) "Focal Sclerosis"
k-14	Syndrome of Renal Vein Thrombosis and Proteinuria (Nephrosis)	
	Generalized-diffuse	epimembranous spikes (membranous glomerulopathy) granular epimembranous deposits epimembranous humps (variable) mesangial sclerosis (variable)
k-15	Glomerular Amyloidosis	
	Generalized-segmental	epimembranous fibrils mesangial deposits (amyloid) mesangial sclerosis
	Focal-segmental	subendothelial deposits
k-16	Waldenstroms Macroglobulinemia-Mixed Cryoglobulinemic GN	
	Focal-segmental	intracapillary thrombi mesangial proliferation mesangial deposits

*Isolated sclerosis may be secondary to vascular or tubulo-interstitial disease
†Deposits involve basement membranes of capillaries, Bowman's capsule, tubules & vessels.

(Continued to next page)

TABLE 2 (Continued)

k-17	Eclampsia	
	Generalized-diffuse	endotheliosis subendothelial fibrin
	Focal	intramembranous deposits (variable) and nonargyrophillic
Lupus Nephritis		
k-18	Glomerulitis Type	
	Focal	mesangial deposits mesangial proliferation subendothelial deposits (variable)
k-19	(Glomerulonephritis-Diffuse) "Active" Type	
	Generalized-segmental	mesangial proliferation mesangial deposits endothelial proliferation
	Focal-segmental	subendothelial deposits granular epimembranous deposits and humps fibrin thrombi tuft necrosis hematoxylin bodies
k-20	Membranous Type (Membranous Glomerulopathy)	
	Generalized-diffuse	epimembranous spikes granular epimembranous deposits epimembranous humps (variable)
k-21	Polyarteritis Nodosa; Wegener's Granulomatosis* (Panarteritis)	
	Focal-segmental	mesangial proliferation endocapillary proliferation tuft necrosis epithelial proliferation (variable)
k-22	Hypersensitivity Angiitis; Churg-Strauss Hypersensitivity Angiitis*	
	Focal-segmental	endocapillary proliferation tuft necrosis fibrin thrombi (variable) epithelial proliferation mesangial proliferation
k-23	Disseminated Intravascular Coagulation, Thrombotic Thrombocytopenic Purpura; Hemolytic-Uremic Syndrome	
	Generalized to focal Segmental	fibrin thrombi tuft necrosis endotheliosis subendothelial fibrin
k-24	Progressive Systemic Sclerosis; Malignant Hypertension	
	Focal-diffuse and segmental	tuft necrosis mesangial sclerosis (non-nodular)
k-25	Lung Hemorrhage—Nephritis (Goodpastures) Syndrome	
	Generalized	epithelial proliferation (hypercellular crescents) tuft necrosis fibrin exudation urinary space mesangial and endothelial proliferation (variable)

*Key-granulomatous interstitial infiltrate (See Table 3).

lary proliferation is accompanied by generalized fibrin thrombi and tuft necrosis (Florid or Fulminant Acute Proliferative Glomerulonephritis). This process must be distinquished clinically and serologically from Lupus Nephritis, glomerulonephritis type, the paraproteinemias, and acute necrotizing processes.

Generalized and *segmental* endocapillary and mesangial proliferation is typical of Lupus Nephritis, active glomerulonephritis (G.N.) type. When this proliferative glomerulopathy is identified, clinical and serologic evidence of S.L.E. should be looked for carefully. Other histologic features frequently support this direction of investigation and occasionally identify Lupus specifically (i.e. the combination of deposits of subendothelial, mesangial and subepithelial regions, hemotoxylin bodies, and rarely LE phenomena within the glomerulus.)

Focal segmental endocapillary hypercellularity is relatively nonspecific and commonly associated with prevalent mesangial proliferation. The differential includes Lupus Nephritis, glomerulonephritis, and glomerulitis types, Anaphylactoid Purpura, endocarditis, Berger's disease, benign recurrent hematuria, and the necrotizing angiitis.

Endotheliosis

Swelling and apparent relative increase in endothelial cells is *generalized* and *diffuse* in pattern in eclampsia; *Focal* and *segmental* endotheliosis is common to a variety of processes with tuft necrosis (e.g. necrotizing angiitis, fibrinothrombotic phenomena). *Focal diffuse* endothelial swelling is usually present in those renal glomeruli undergoing necrosis in progressive systemic sclerosis (Scleroderma) and malignant hypertension.

Mesangial Proliferation

Mesangial hypercellularity is by far the most common and the least specific of cellular alterations identified in glomerular disease. *Generalized* and *diffuse* proliferation is common to chronic glomerulonephritis of many types and the microscopist must seek other changes for a possible clue to etiology. Also, as noted above, generalized mesangial hypercellularity may persist for many months following acute proliferative glomerulonephritis and might only be distinguishable from

TABLE I-B
Glomerular Lesions—Distribution in Disease
Membranous (Deposits)
Clinical Differential Diagnosis Worklist

Generalized		Focal	
diffuse	segmental	diffuse	segmental
SUBENDOTHELIAL		(Subendothelial fibrin)	Lupus Nephritis, Glomerulonephritis & Glomerulitis types (k-18, 19)
Lupus Nephritis	Lupus Nephritis, Glomerulonephritis type (k-19)	Necrotizing Glomerulonephritis (k-21, 22)	Amyloidosis (k-15)
Glomerulonephritis type (rare) (k-19)	Chronic G.N., (non spec)	Malignant Hypertension	Chronic G.N. (non spec) (k-8)
Eclampsia (k-17)		P.S.S., (k-24)	
(subendothelial fibrin)			
INTRAMEMBRANOUS-MESANGIAL			(common)
Non Argentophillic			
Chronic mesangio-capillary G.N. (k-9)	Lupus Nephritis, Glomerulonephritis type (k-19)	Chronic Sclerosing G.N.	Anaphylactoid Purpura (k-6)
Chronic Lobular G.N.	Chronic G.N. (non spec)	Focal Sclerosing G.N. (k-8)	Lupus Nephritis, glomerulitis
		Chronic G.N. (non spec)	Chronic G.N., all types (k-8)
			Healed Acute Prolif. G.N. (k-2)
			Healed Necrotizing G.N. (all types)
Argentophillic		(common)	
Renal Membranous Nephropathy (k-10)		Focal scarring secondary to vascular, glomerular or tubulo-interstitial disease	
(*deposits of "Dense Deposit Disease")			
EPIMEMBRANOUS			
(Subepithelial)			
Spike-deposits (gen.-chronic immune complex process)		Chronic G.N. non specific (antecedent chronic immune complex disease)	
Idiopathic Membranous G.N. (k-12)			
Lupus Nephritis, Membranous type (k-20)			
Renal Vein Thrombosis, nephrosis (k-14)			
Diabetes, Protozoal, Mercury			
Humps		Non specific immune complex process (Acute and Chronic G.N.)	
Acute Proliferative G.N. (e.g. Post strep) (k-1)			
(gen—acute immune complex process)			
Fibrils		Glomerular Amyloid (k-15)	
Glomerular Amyloid (k-15)			

chronic glomerulonephritis with time.

Focal diffuse or *segmental* mesangial hypercellularity is also common to a variety of diseases, in particular, collagen vascular diseases and allergic glomerulitus. (e.g. Lupus Nephritis, glomerulonephritis and glomerulitis types, Anaphylactoid Purpura, necrotizing angiitis, etc.) Focal segmental mesangial hypercellularity is almost always accompanied by mesangial deposits in similar distribution.

Epithelial Proliferation

Generalized hypercellular crescents define a poor prognosis if not a specific etiology. These lesions are common to the "rapidly progressive (malignant) glomerulonephritis" syndromes. These hypercellular crescents are accompanied by varying degrees of tuft necrosis and fibrin exudation into the urinary space. Idiopathic rapidly progressive glomerulonephritis, Goodpastures' disease or syndrome, and *malignant Anaphylactoid* Purpura are frequently inseparable morphologically.

Hypercellular crescents are focal early and generalized late in Wegener's granulomatosis. The vasculitis and interstitial granulomatous infiltrate with periglomerular accentuation, are histologically more typical. A summary of other helpful clinical and histologic findings are included in Table 3.

Anti GBM antibodies (Goodpastures' disease) are not demonstrable by the light microscopic techniques demonstrated here and require direct antibody studies. The subepithelial humps of immune complex related rapidly progressive glomerulonephritis are demonstrable by these techniques. *Focal hypercellular crescents* are common to a variety of necrotizing glomerulonephritis and correspond discretely with areas of tuft necrosis and fibrin exudation into the urinary space.

Fibrous and *fibrocellular crescents* are common in chronic glomerulonephritis in late stages and are nonspecific. *Focal* fibrous crescents are frequent in healed and quiescent processes. Also, nonglomerular diseases frequently result in focal fibrous crescents and periglomerular scarring (tubulo-interstitial disease, arteriosclerotic vascular disease, etc.)

Epithelial Cell Swelling ("podocytosis")

This is a light microscopic phenomenon with a high degree of correlation with foot process fusion and proteinuria. *Normal* glomerular capillary basement membranes (i.e. no epimembranous deposits) with generalized diffuse epithelial swelling are typical of lipoid nephrosis. The epithelial cells appear swollen and increased; *"podocytosis"* is therefore descriptive as an extracapillary counterpart of *"endotheliosis"*.

Electron microscopy or direct immunofluorescence are preferred to identify the epimembranous deposits of membranous glomerulopathy and differentiate that abnormality from lipoid nephrosis *not* foot process fusion. Foot process fusion per se is a nonspecific alteration and common in all instances of significant proteinuria. This epithelial swelling is present in all instances of nephrosis and demonstration of associated membranous and/or mesangial alterations is more meaningful in differentiating the disease processes responsible (Table 4).

Membranous Abnormalities (Table 1-B)

Subendothelial Deposits

Subendothelial deposits in *generalized* and *segmental* distribution are common in Lupus Nephritis, glomerulonephritis type but are not diagnostic of that disease. The distribution of this abnormality is similar to the endocapillary proliferation.

Generalized diffuse subendothelial deposits are rare but do occur in a small percent of patients with Lupus Nephritis, glomerulonephritis type. Fibrin is present in this distribution in the well developed eclampsia lesion. *Focal* subendothelial deposits are relatively common in glomerular

TABLE 3
Necrotizing Angiitis-Pathergic Granulomatosis

	Renal	Lung	Vessels	Granulomas*	Eosinophillia
Polyarteritis Nodosa	+++	+	AA.	—	—
Hypersensitivity Angiitis	+++	++++	aa., vv.	—	++++
Wegener's Granulomatosis	++	++++	AA., VV.	++++	+
C.S. Allergic Granulomatous Angiitis	++++	++++	aa., vv.	+++	++++

*Extravascular

disease and are nonspecific.

Intramembranous Deposits

Nonargentophilic intramembranous deposits, when *generalized* and *diffuse* in distribution, are typical of chronic mesangio-capillary or chronic hypocomplementemic membranoproliferative glomerulonephritis. *Focal* and/or *segmental nonargenophilic* intramembranous deposits are nonspecific.

Generalized and *diffuse argentophilic* intramembranous deposits are typical of so-called "dense deposit disease" or renal membranous nephropathy. The deposits frequently involve the basement membrane of the glomerular capillaries, Bowman's capsule, renal tubules and vessels. *Segmental* or *focal argentophilic intramembranous* deposits are relatively nonspecific and found in a variety of glomerulopathies and in areas of focal scarring secondary to vascular or tubulointerstitial disease.

Epimembranous (Subepithelial) Deposits

When the typical subepithelial membranous *spike lesion* is identified in *generalized* distribution a specific morphologic diagnosis is indicated (i.e. membranous glomerulopathy). By inference the disease is a chronic immune complex process. In the vast majority of instances the etiology of this process is unknown or "idiopathic." Identical morphology is found in approximately 10% of patients with Lupus Nephritis, membranous type and the nephrotic syndrome. Similar morphology is identified in individuals with renal vein thrombosis with nephrosis and small percentage of patients with diabetes.

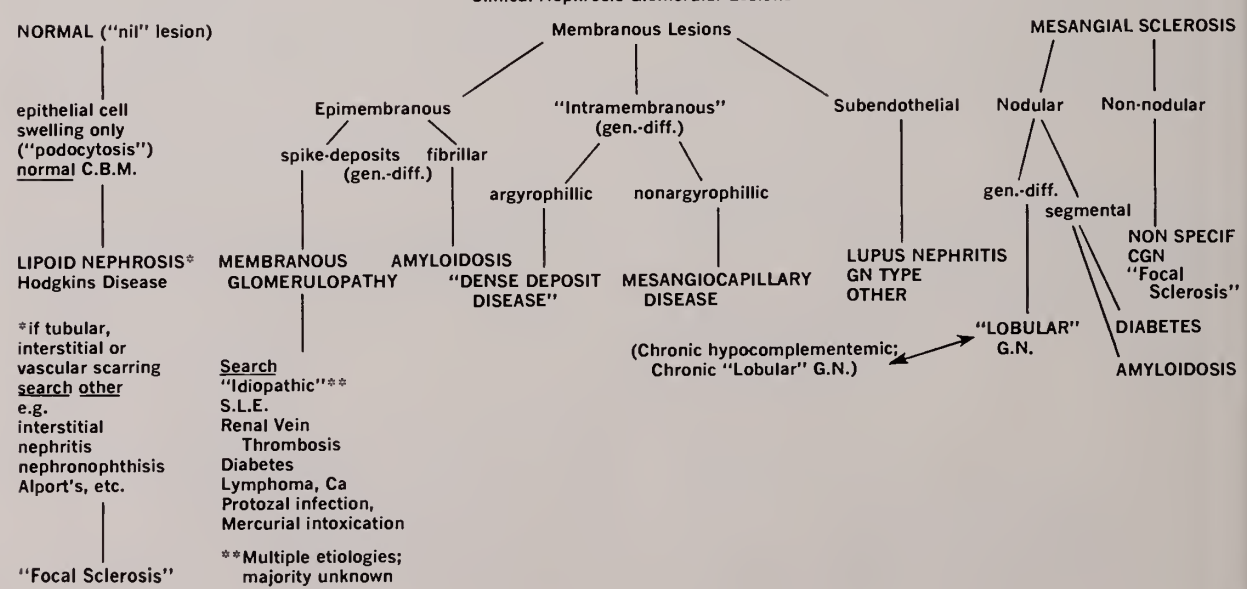
Generalized epimembranous humps with generalized diffuse endocapillary proliferation is typical of acute proliferative glomerulonephritis, regardless of the etiology, when the insult is an acute immune complex process. *Focal* epimembranous deposits, *spikes* and *humps* are not uncommon with acute and chronic processes and indicate the presence of an antecedent immune complex disease.

Subepithelial or epimembranous silver positive fibrillar masses are typical of Amyloidosis. This abnormality is apparently specific.

Mesangial Sclerosis (Table 1-C)

Generalized diffuse nodular mesangial sclerosis is typical of the late stages of mesangiocapillary disease or chronic lobular glomerulonephritis. *Generalized segmental nodular mesangial sclerosis* is common in Diabetes and less frequent in Amyloidosis. *Focal segmental modular mesangial sclerosis*

TABLE 4
Clinical Nephrosis-Glomerular Lesions



is more typical of Amyloidosis.

Non-nodular mesangial sclerosis is relatively nonspecific, regardless of distribution, and may be secondary to a variety of extraglomerular processes.

Tuft Necrosis (Table 1-D)

Generalized diffuse tuft necrosis usually results from major vessel injury with large areas of parenchymal infarction. More commonly tuft necrosis is generalized and segmental in distribution as with disseminated intravascular coagulopathy, thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Generalized and segmental tuft necrosis is frequent in lupus nephritis, glomerulonephritis *type* and rapidly progressive GN syndromes.

Focal and *diffuse tuft necrosis* is relatively typical of the glomerular lesion noted in the late stages of malignant hypertension and progressive systemic sclerosis involving those glomeruli with severe vascular involvement and necrosis.

Focal and segmental distribution of tuft necrosis is probably the least specific, but is more typical of lupus nephritis *GN* type, anaphylactoid purpura and allergic angiitis.

Intracapillary Fibrin (Hyalin) Thrombi (Table 1-E)

Generalized and *diffuse* capillary thrombi are present in disseminated intravascular coagulation in adults and hemolytic uremic syndrome in children. Similar distribution is occasionally identified in individuals with so-called florid or fulminant acute proliferative glomerulonephritis and thrombotic thrombocytopenic purpura.

Focal and *segmental* thrombi are more typical of T.T.P. but this distribution is also commonly identified with lupus nephritis, glomerulonephritis type, mixed cryoglobulinemic glomerulonephritis and Waldenstrom's macroglobulinemia.

Thankfully, the microscopist does not depend upon morphology alone to determine pathophysiology, etiology, or prognosis. Extraglomerular pathology, extrarenal histology (if available), clinical history, physical, and laboratory findings all add to the final assessment. Increasing numbers of relatively simple serologic tests have added

TABLE I-C
Glomerular Lesions—Distribution in Disease
Mesangial Sclerosis
Clinical Differential Diagnosis Worklist

Generalized		Focal	
–diffuse	–segmental	–diffuse	–segmental
Nodular			
Chronic Lobular G.N. (k-9) (Chronic mesangiocapillary)	Diabetes (k-11)	Diabetes (k-11) Amyloid (k-15)	Diabetes (k-11) Amyloid (k-15)
Non Nodular			
End Stage Renal Disease (non spec.) Chronic Sclerosing G.N. (k-8) Diabetes (k-11)	Chronic G.N., (non spec.)	Focal scarring secondary to vascular, glomerular or tubulo-interstitial disease	Anaphalactoid Purpura (k-6) Healed Necrotizing glomerulitis Lipoid Nephrosis (k-13) (juxta medullary) Diabetes (k-11) Chronic G.N. all types (k-8) Healed G.N. all types Aging, non spec.

TABLE I-D
Glomerular Lesions—Distribution in Disease
Intracapillary Fibrin (Hyaline) Thrombi
Clinical Differential Diagnosis Worklist

Generalized		Focal	
diffuse	segmental	diffuse	segmental
D.I.C., H.U.S. (k-23) Florid Acute Prolif. (k-3) G.N. with intracapillary fibrin thrombi	D.I.C., T.T.P., H.U.S. (k-23) Lupus Nephritis, glomerulonephritis type (k-19) Necrotizing angiitis, glomerulitis (k-21, 22) Rapidly Progressive G.N. (k-4) Polyarteritis Nodosa (k 21) Wegener's Granulomatosis	Necrotizing Angiitis (k-21, 22)	T.T.P., D.I.C., H.U.S. (k-23) Lupus Nephritis, Glomerulonephritis type (k-19) Mixed cryoglobulinemic (k-16) glomerulonephritis Waldenstrom's Macroglobulinemia Acute and Chronic G.N. Necrotizing glomerulitis, Angiitis (k-21, 22) Rapidly Progressive G.N. (k-4)

significantly to evaluation of clinical disease (e.g. depressed serum complement levels and elevated titers of antibody to streptococcal antigens in a patient with acute glomerulonephritis essentially preclude the need for renal biopsy in the uncomplicated case. Demonstration of anti-native DNA antibodies in a patient with Lupus Nephritis is a more specific means of documenting that etiology than tireless search for hematoxylin bodies in the biopsy; the biopsy is performed to determine the *type* of Lupus Nephritis present, *not* that the patient has S.L.E.)

Summary

A review of glomerular light microscopic anatomy and pathology including a program for definition of a morphologic diagnosis is presented. A systematic method of deriving a etiologic differential diagnosis from this morphologic diagnosis is proposed.

This form of independent objective anatomic deduction is felt to be of more benefit than microscopic judgment based on clinical bias. Ultimately, independent morphologic and clinical interpretations must be considered together for an accurate conclusion.

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Technical Notes

The following is an outline of the routine processing and staining techniques used in our laboratory. Included are our reasons for recommending these procedures:

1. Fixation: —fresh buffered formalin. Buffered formalin is, or at least should be, a universally available fixative. Helley's is an excellent fixative for the Jones' periodic acid methenamine silver stain but is not as desirable for other staining techniques. We have found buffered formalin fixation superior for trichrome stains in particular.
2. Embedding: High melting point paraffin (60-62 C.*) This is an absolute necessity for thin sections. Epoxy embedded tissue may be cut at closer intervals for thin sections, but is less desirable for some staining techniques. We have had good results cutting thin sections for all special stains with tissue embedded in high melting point paraffin.
3. Tissue Cutting:
   . . . routine hematoxylin and eosin—3 micra.
   . . . Masson trichrome—3 micra.
   . . . Jones' periodic acid methenamine silver—1-2 micra.
   . . . Amyloid—6 micra.
   1-2 micra sections are de .. for the Jon .ain; thicker sections may be ..dequate but generally are not as helpful. A good microtome and a sharp knife are of utmost importance.
4. Tissue Staining:
   a. Hematoxylin and eosin—routine.
   b. Masson trichrome. We prefer the Masson trichrome over other azofuchsin methods for no objective reason. We recommend doubling the Biebrich scarlet reaction time. It is important to use fresh scarlet.
   c. Jones' periodic acid—methenamine silver stain:
   d. Amyloid stain: "Thick" sections are generally preferable for crystal violet and congo red preparations. We recommend demonstration of epimembranous fibrils with the Jones' silver stains (thin sections).
5. Slide Review: We recommend allotting ample time for review of all glomeruli under oil immersion to demonstrate deposits and other abnormalities of the basement membrane and mesangium.

*Bioloid; Will Scientific Inc.

Comment

We feel the combination of separate trichrome and silver preparations is preferable. The silver technique is preferred for structural abnormalities of the capillary basement membrane and mesangium, mesangial sclerosis, subepithelial spikes, and demonstration of amyloid fibrils. Subendothelial, epimembranous, and mesangial deposits and fibrin stain red with the trichrome stain. The deposits are most often silver negative. The periodic acid Schiff-Hematoxylin stain differentiates none of these lesions as well.

TABLE I-E
Glomerular Lesions—Distribution in Disease
Tuft Necrosis
Clinical Differential Diagnosis Worklist

Generalized		Focal	
diffuse (rare)	segmental	diffuse	segmental
Acute major vessel injury	D.I.C., T.T.P., H.U.S. (k-23) Lupus Nephritis glomerulonephritis type (k-19) Necrotizing angiitis, glomerulitis Rapidly Progressive G.N. (k-4) Polyarteritis Nodosa (k-21) Wegener's Granulomatosis (k-21)	Malignant Hypertension Progressive Systemic Sclerosis (P.S.S.) (k-24) Necrotizing Angiitis (k-21, 22)	T.T.P., S.B.E. (k-23) Lupus Nephritis, glomerulonephritis type (k-19) Anaphalactoid Purpura (k-6) Hypersensitivity Angiitis (k-22)

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BUILDING NEW CLINIC IN BROOKLYN PARK—A Minneapolis suburb of 30,000 population. *This 12 to 15 physician clinic is scheduled for occupancy in July 1975. *We solicit the physicans input regarding his space layout and decorating scheme prior to construction. *This facility will be of the highest quality at the lowest possible sq. ft. cost. For leasing or other information contact: Rick Brendsel or Dick Mueller, Real Estate 10, Inc. Commercial-Investment Division, 7420 Unity Avenue North, Minneapolis, Minnesota 55443. (612) 566-6028.

OCEAN FRONT APARTMENTS—2 Florida physicians will rent luxury ocean front condominium apartments—Daytona area. 2 BR, 2 bath, pool, sauna, tennis, golf nearby. Disney World 1 hour via Interstate. Excellent for summer family vacation also. 904-373-7064 or 904-372-5467—evenings.



Putting out the fires of arthritic pain

Rheumatoid arthritis can sometimes spread like wildfire, with joint after joint going up inflamed: "The usual onset is manifested by spotty joint involvement but an acute onset of symmetrical polyarthritis may be noted."[1]*

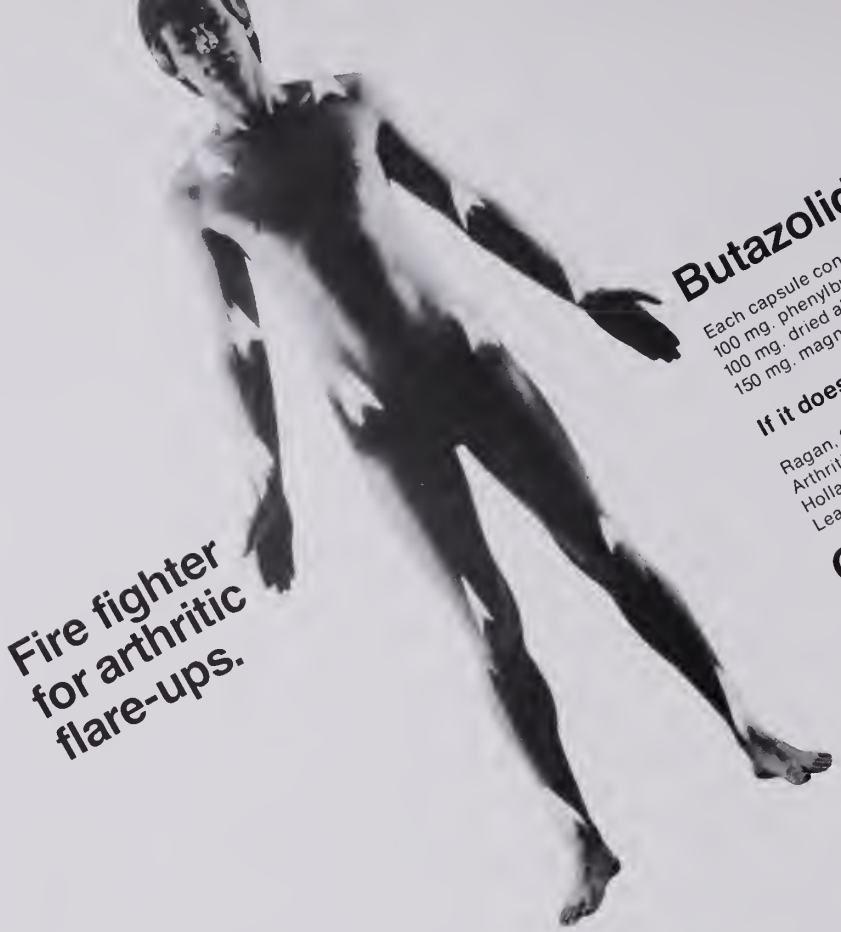
If aspirin fails, consider Butazolidin alka. Giving one capsule four times a day often provides prompt, pain-relieving, anti-inflammatory action to help restore joint mobility. The results you can get within a week can be maintained on as little as one or two capsules daily.

Serious side effects can occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings, contraindications and adverse reactions. For full details, please read the prescribing information. It's summarized on the back of this page.

Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.



Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.

Ragan, C.: The Clinical Picture of Rheumatoid Arthritis, in Arthritis, ed. 8, edited by J. L. Hollander and D. J. McCarty, Jr., Philadelphia, Lea & Febiger, 1972, chap. 21, p. 335.

Geigy

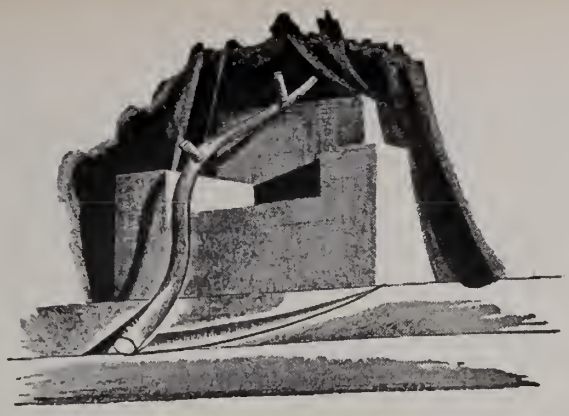
Fire fighter for arthritic flare-ups.

Important Note: This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Substitute alka capsules for tablets if dyspeptic symptoms occur. Patients should discontinue the drug and report immediately any sign of: fever, sore throat, oral lesions (symptoms of blood dyscrasia); dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.
Indications: Rheumatoid arthritis, osteoarthritis, bursitis, acute gouty arthritis and rheumatoid spondylitis.
Contraindications: Children 14 years or less, senile patients; history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia, history or presence of drug allergy, blood dyscrasias; renal, hepatic or cardiac dysfunction; hypertension; thyroid disease; systemic edema, stomatitis and salivary gland enlargement due to the drug; polymyalgia rheumatica and temporal arteritis; patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.
Warnings: Age, weight, dosage, duration of therapy, existance of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.
Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight, complete weekly (especially for the aging) or an every two week blood check, pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia; ulcerative stomatitis, salivary gland enlargement.
(B)98-146-070-J (10/71)

For complete details, including dosage, please see full prescribing information.

GEIGY Pharmaceuticals
Division of CIBA-GEIGY Corporation
Ardsley, New York 10502

BU 10259



In Memoriam

RALPH LORMAR OLSEN, M.D.

Dr. Ralph L. Olsen, 71, St. Paul physician and surgeon for thirty-five years, died October 17th. He was on the medical staff of Bethesda Lutheran Hospital, where he had served as chief of staff.

Dr. Olsen was a Fellow in the American Academy of Family Physicians and a member of the Ramsey County Medical Society, Minnesota State Medical Association and the American Medical Association.

He was survived by his wife, Edith, and daughters, Carolyn and Beverly.

MATTHEW A. EICH, M.D.

Dr. Matthew A. Eich, Minneapolis obstetrician and gynecologist, died September 17th. He was a Life Member of the Minnesota State Medical Association and a member of the Hennepin County Medical Society and the American Medical Association.

JAMES A. JOHNSON, M.D.

Dr. James A. Johnson, 91, Minneapolis surgeon, died September 24. He was a founder of the Nicollet Clinic and a first director of the Cancer Institute at the University of Minnesota.

Dr. Johnson, the son of Danish immigrants, grew up on a farm near Sparta, Wisconsin. He graduated from the Northwestern University Medical School. Dr. Johnson was a member of the Hennepin County Medical Society and American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

His wife, Esther, and two daughters, Betty and Katherine, survive him.

ARTHUR P. LAPIERRE, M.D.

Dr. Arthur Lapierre, 77, Minneapolis physician, died July 24. He had attended the University of Minnesota Medical School.

Dr. Lapierre was a member of the Hennepin County Medical Society and the Minnesota State Medical Association.

He was survived by his wife, Margaret. Dr. Maurice G. Lapierre of Minneapolis is a surviving brother.

STEVEN E. STARYK, JR. M.D.

Dr. Steven E. Staryk, Jr., 28, resident at the Mayo Clinic, died September 11th. He had obtained his medical education at the Wayne State University Medical School, Detroit.

Dr. Staryk was a resident member of the Zumbro Valley Medical Society, the American Medical Association and the Minnesota State Medical Association.

HARRIS F. BUNNELL, M.D.

Dr. Harris F. Bunnell, 61, Winona psychiatrist, died September 27, of a heart attack at his home.

Born at Toppenish, Washington, his medical education was obtained from the University of Oregon Medical School, Portland.

He was a member of the American Medical Association, the Winona County Medical Society, the Minnesota Psychiatric Society, Association of Medical Superintendents of Mental Hospitals, the Minnesota State Medical Association and was a Fellow of the American Psychiatric Association.

His wife, Esther, son, Ronald, and two daughters, Helen and Lynn survive him.

WILLIAM B. RICHARDS, M.D.

Dr. William Richards, 77, St. Cloud physician, died May 9. He had attended the University of Minnesota Medical School and started practicing medicine in St. Cloud in 1926.

Dr. Richards was a member of the Stearns-Benton County Medical Society and the American Medical Association and a Life and 50 Club Member of the Minnesota State Medical Association.

MAX SEHAM, M.D.

Dr. Max Seham, Minneapolis pediatrician and University of Minnesota professor emeritus, died October 15. He was born in Lithuania and came to the United States in 1894.

In addition to practicing privately for more than 60 years, Dr. Seham had been chief of staff at Abbott, Northwestern and Mount Sinai Hospitals and director of the Lymanhurst Heart Clinic. He also was a former director of the Children's Heart Clinic at Hennepin County General Hospital. Dr. Seham was a member of the Hennepin County Medical Society, the American Medical Association, and a Life and 50 Club Member of the Minnesota Medical Association.

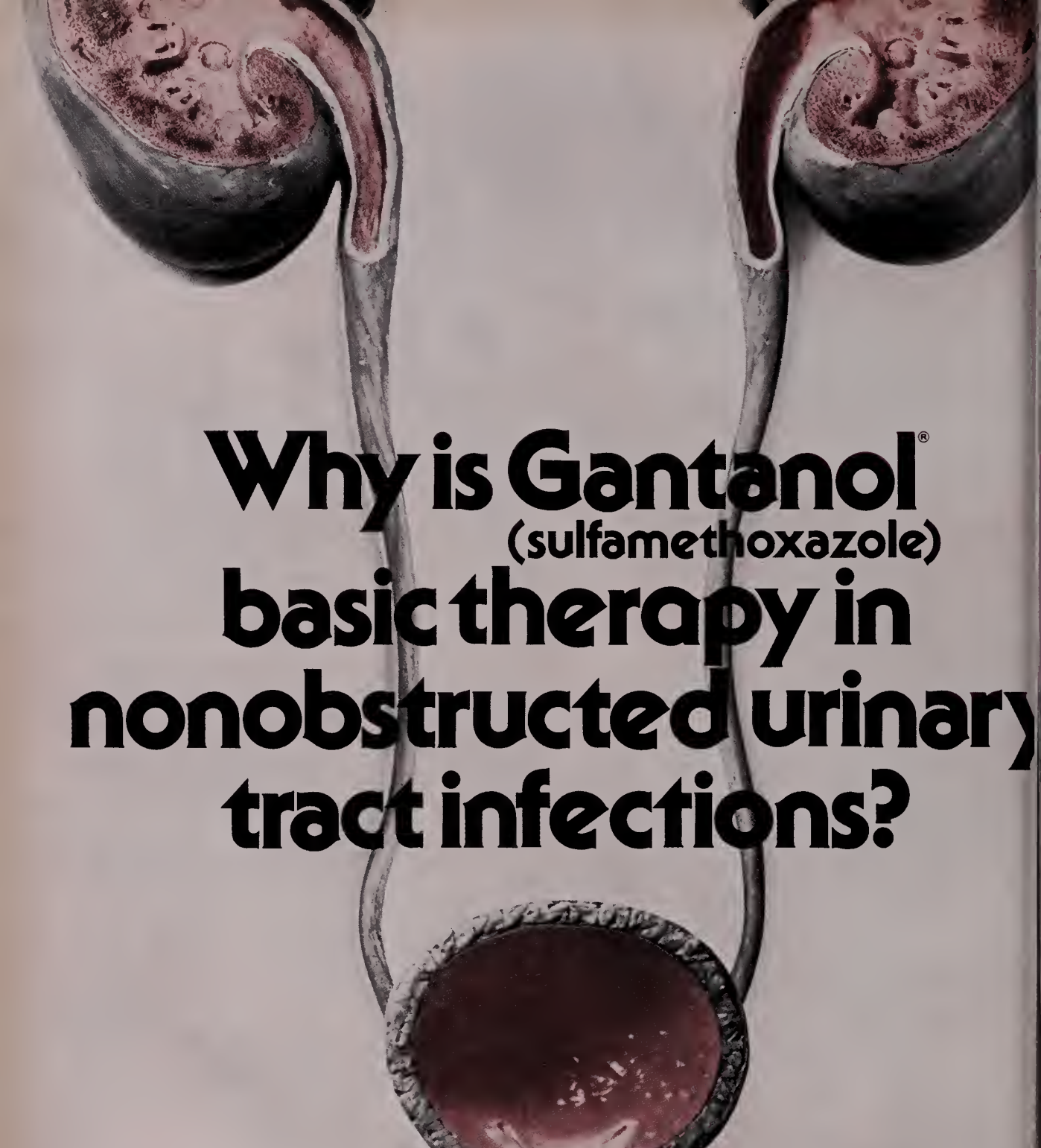
His wife, Elsie, and son, David, survive him.

FRANK EDWARD MORK, M.D.

Dr. Frank E. Mork, a long-time physician in Anoka, died of a heart attack on August 6. He started his medical practice in Anoka in 1931 and retired in 1972. A graduate of Creighton Universtiy School of Medicine in Omaha, he interned at St. Mary's Hospital in Minneapolis. He was the elected first Chief of Staff of the New Mercy Hospital in 1965.

Dr. Mork was a member of the American Medical Association, Hennepin County Medical Society, and the American Academy of Family Physicians and was an Associate Member of the Minnesota State Medical Association.

His wife, Loretta, daughter, Mrs. John McNeely, and son, Dr. Frank E. Mork, Jr. survive him.



Why is Gantanol® (sulfamethoxazole) basic therapy in nonobstructed urinary tract infections?

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or vent sequelae (rheumatic fever, glomeruloneph of such infections. Deaths from hypersensitivity r tions, agranulocytosis, aplastic anemia and other b dyscrasias have been reported and early clinical signs (throat, fever, pallor, purpura or jaundice) may indicate se blood disorders. Frequent CBC and urinalysis with microsc examination are recommended during sulfonamide therapy. Ins cient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired ren hepatic function, severe allergy, bronchial asthma; in glucos phosphate dehydrogenase-deficient individuals in whom d related hemolysis may occur. Maintain adequate fluid intak prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, a tic anemia, thrombocytopenia, leukopenia, hemolytic anemia,

Because it is considered a good choice...

- for efficacy in nonobstructed cystitis, pyelonephritis and pyelitis
- for control of susceptible *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris*
- for prompt antibacterial blood and urine levels in from 2 to 3 hours after initial 2-gram adult dose
- for economical around-the-clock coverage
- for maximum patient cooperation with easy-to-remember B.I.D. dosage

Basic Therapy

Gantanol®

(sulfamethoxazole)

Tablets/Suspension
(0.5 Gm) (0.5 Gm/teasp.)

a, hypoprothrombinemia and methemoglobinemia); *allergic ctions* (erythema multiforme, skin eruptions, epidermal necrolyurticaria, serum sickness, pruritus, exfoliative dermatitis, analactoid reactions, periorbital edema, conjunctival and scleral ction, photosensitization, arthralgia and allergic myocarditis); *trointestinal reactions* (nausea, emesis, abdominal pains, hepa-, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* adache, peripheral neuritis, mental depression, convulsions, xia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous ctions* (drug fever, chills, toxic nephrosis with oliguria and uria, periarteritis nodosa and L.E. phenomenon). Due to certain emical similarities with some goitrogens, diuretics (acetazolade, thiazides) and oral hypoglycemic agents, sulfonamides have used rare instances of goiter production, diuresis and hypoglymia as well as thyroid malignancies in rats following long-term ministration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

ROCHE

Roche Laboratories
Division of Hoffmann-La Roche Inc.
Nutley, N.J. 07110

Book Reviews

SOUND SEX AND THE AGING HEART—Lee D. Scheingold and Nathaniel N. Wagner. Human Sciences Press. 168 pages. Price $7.95. 1974.

Scheingold and Wagner and Robert Levenson, M.D., a cardiologist, have interested themselves in sexual activity as studied in a cardiac work evaluation unit. They are in charge of the Washington State Unit in Seattle.

They describe the benefits of sex in the later years and in general expand upon the advice physicians are called upon to give re sex to his cardiac patient. It is evident that the authors agree that sex is here to stay and sexual activity is possible and probably beneficial to cardiac patients.

Physicians might well consider this book as a prescription to anxious patients who wish to have precise advice concerning their sexual activity following cardiac illness, and no doubt many patients can benefit from 168 pages of such advice.

The book is written for the patient and in terms that he can understand. Lee Scheingold is a psychologist and N. N. Wagner is a Ph.D., specializing in medical psychology and family planning. It seems to me that information concerning these qualifications are all important and should be included in the text and not simply relegated to the dust cover.

Reuben Berman, M.D.
Editor Emeritus

CLINICAL LABORATORY METHODS, by John D. Bauer, Philip G. Ackerman, and Gelson Toro, The C. V. Mosby Company, 1974, Price $20.00.

Books are like rivers.

Some you dangle in and get only your feet wet. Some you plunge into and let the current sweep you away. Some you float on the surface and let cool logic sooth your underside. And some you just sit on the bank and let the narrative flow by.

This is a foot-dangler's book for pathologists (or anyone else in the laboratory). If you want to dip into an encyclopedic book to find how, why, and when to do a laboratory procedure, then this is the book for you.

Perhaps the greatest two virtues of this book are: 1) its store of recent information; and 2) its excellent tables, drawings, and photographs. As far as I'm concerned, its greatest faults are its passive prosaic prose and its lack of interpretive depth.

Richard C. Reece, M.D.
Editor-in-Chief

STRESS DISEASE, THE EMOTIONAL PLAGUE, by Peter Blythe, 168 pp, $5.95, St. Martin's Press, 1973.

The author, a senior lecturer in psychology and hypnotherapy, has written a compendium on medical psychodynamic theories. As such, this book contains useful information of interest to all physicians. Unfortunately, the author has an anti-medical bias and makes the usual mistake of the non-medical therapist in quoting everyone from Freud through Sullivan and then denying that physicians have any understanding of psychodynamics. Further, the title of the book suggests that the author has some central theme in his approach; however, the reader will find a disorganized collection of mutually contradictory theories and approaches. In all fairness, this is the current state of our knowledge and the author's attempts to synthesize this knowledge into a simple rubric of "emotional plague" must be forgiven. What is hard to forgive are some of his statements such as, "Medical training does not include an in-depth study of psychodynamics." Further, Mr. Blythe has almost a childlike faith in the printed word. Apparently, he accepts without reservation claims that a third of all flat-chested women will have their breasts enlarged by Janov's Primal Scream Therapy.

This book is interesting reading and can serve as an introduction to a wide variety of theories and speculations about the human condition. It is not a "how-to-do-it manual" or an acceptable textbook. A physician interested in becoming acquainted with a variety of psychological approaches and theories could begin with this book.

James Janecek, M.D.
St. Paul, Minnesota

ARTHRITIS by Sheldon Paul Blau, M.D. and Dodi Schultz. $5.95. Doubleday and Company, Inc., 164 pages, Garden City, N.Y., 1974.

This small volume is loaded with information and, in fact, this may be its problem. The authors very carefully and clearly define and describe the major arthritic conditions but in such detail that the uninitiated reader may find himself "over his head." Rheumatoid arthritis, osteoarthritis, and gouty arthritis are well-presented but the level of the material seems to ask for more background. Granted that the subject matter is difficult, yet the book probably requires both directional and interpretive guidance from the physician. And this may well be the proper way to use this volume as an adjunct to patient care.

Those sections which deal with direct advice and counsel to the afflicted individual are clear, concise and sound. Those portions which describe treatment modalities, including a long chapter on drug therapy are well done.

John V. Thomas, M.D.
Duluth, Minnesota
(Continued on page 103.)

adjunctive therapy for wound debridement

HELPS TO REMOVE:

- Necrotic Tissue and Associated Odor

HELPS PREPARE WOUND FOR:

- Granulation/Healing
- Granulation/Grafting



CLEANSE WOUND
Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials.



THOROUGHLY MOISTEN
Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g., sodium chloride or water solutions).



APPLY ENZYME
Apply a layer of TRAVASE Ointment. Assure intimate contact with necrotic tissue and complete wound coverage.

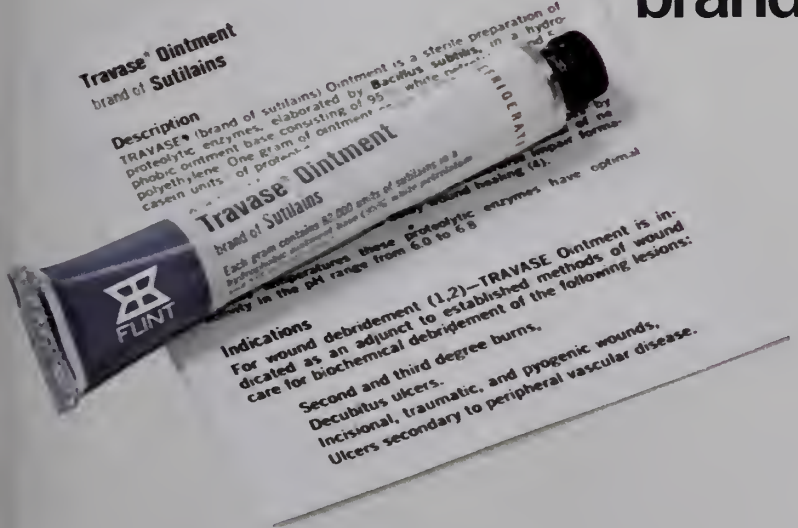


APPLY MOIST DRESSING
Apply loose moist dressings (most important with dry leathery eschar).



CHANGE DRESSINGS
When changing dressing, gently wipe away the dissolved material. Repeat the procedure, including application of TRAVASE Ointment, 3 to 4 times per day for best results.

Travase® Ointment
brand of Sutilains



FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC
Deerfield, Illinois 60015

Please see next page for prescribing information.

Travase® Ointment brand of Sutilains

ulcers

TERRY V. CARLE, M.D., CLINICAL INSTRUCTOR, DEPT OF PHYS. MED. & REHAB., CRAIG REHABILITATION HOSPITAL, UNIVERSITY OF COLORADO



Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



After nine days of TRAVASE therapy, debridement is nearly complete and granulation evident.

burns

DALE B. DUBIN, M.D., DIPLOMATE, AMERICAN BOARD OF PLASTIC SURGERY, TAMPA, FLORIDA



Before treatment . . .



48 hours following treatment with TRAVASE Ointment on right hand; left hand is control.

Travase® Ointment

(brand of Sutilains)

Indications: For wound debridement, TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

- Second and third degree burns,
- Decubitus ulcers,
- Incisional, traumatic, and pyogenic wounds,
- Ulcers secondary to peripheral vascular disease.

Contraindications: Application of TRAVASE Ointment is contraindicated in the following conditions:

- Wounds communicating with major body cavities,
- Wounds containing exposed major nerves or nervous tissue,
- Fungating neoplastic ulcers,
- Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE upon the developing fetus.

Warning: Do not permit TRAVASE Ointment to come into contact with the eyes. If contact is made, immediately rinse with copious amounts of water, preferably sterile.

Precautions: A moist environment is essential to optimal activity of the enzyme. Enzyme activity may also be impaired by certain agents (see package insert). Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

Adverse Reactions: Consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

DOSAGE AND ADMINISTRATION: STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECTIVE RESULTS OF TREATMENT:

1. Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., hexachlorophene, silver nitrate, benzalkonium chloride, nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g. sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC
Deerfield, Illinois 60015

Legislature

Statement of
The Minnesota State Medical Association

in response to the draft proposal for the
MINNESOTA COMPREHENSIVE HEALTH CARE ACT OF 1975

Presented to the Senate Health Subcommittee—December 10, 1974 by C. A. Anderson, M.D., Chairman, Committee on Public Policy.

A bill drafted for introduction in the 1975 state legislature entitled the Minnesota Comprehensive Health Care Act of 1975 would provide state (public utility type) regulation over much, if not most, of the health care delivery system. This would be accomplished through the creation of a 13 member "health service policy board," including one M.D., appointed by the Governor which would have vast regulatory authority.

The proposed board's powers and duties would include: certification of need; hospital and nursing home rate regulation; authority to approve contracts between health care facilities and third party payors; approval of contractual or other financial arrangements between physicians and health care facilities: licensure and regulation of all health care facilities; authority to conduct audits, investigations, inquiries and hearings on any aspect of health care pertinent to the Act; long-range health planning; rule making authority; and, finally, the board could "exercise all other powers which are reasonably related to the effective implementation of this Act".

The following presentation was made by Chester A. Anderson, M.D., Chairman, MSMA Committee on Public Policy on December 10th before the Senate Health Subcommittee as an official response of the Association to this proposed legislation.

The concern for the health of the people of this state is shared by all of us—providers, consumers and legislators. This concern has repeatedly through the years been coupled with activities which have placed Minnesota among the leaders in providing needed services and ensuring a good life for its residents.

The quality of health care has been a major factor in the high assignment Minnesota has consistently received in national rankings in state "quality of life" assessments. According to a publication issued by the Minnesota Department of Economic Development, Minnesota is rated as Number 1 in the quality of health care of all the 50 states.

This same quality of care for health problems has also been reflected many times by the *low* percentage of people statewide who see health care as a major state problem. Just a year ago, the Minnesota Poll showed that only 5% rated health care as a concern.*

*Minneapolis Tribune, October 28, 1973.

Admittedly, our system is not perfect. There are identifiable problems among certain population groups and in certain geographic locations which need attention. But radical changes aimed at solving localized problems may in turn, ironically, disrupt a health system that generally works and result in diminishing those health services which are effective.

The protection of the health of the citizens of this state is an admirable and worthwhile objective and physicians are the first to support efforts to ensure a healthy people. But health is not necessarily synonymous with health care, although today our society mistakenly uses these terms interchangeably. Many of the problems affecting health conditions are not the result of accessibility, availability or cost of care. Rather they involve environmental conditions and personal life styles. They include problems of housing, poor living conditions, hunger, work environments, automobile and home accidents, etc. They involve genetic conditions and personal habits like smoking,

alcohol and nutrition. Certainly these areas need attention and new and more effective approaches and solutions.

In consideration of the above, the Minnesota State Medical Association feels that the legislature should be more fully aware of the possible implications and ramifications of the provisions of this Comprehensive Health Care Act of 1975, and we hope that careful consideration will be given to our comments.

1. Health care services should be accessible to all persons in the state, and medical care providers have been and will continue to be supportive of new, innovative and realistic approaches to solving the gaps existing in Minnesota. However, there is no single answer nor organizational structure which can unilaterally meet all the localized needs. As examples:

Some 50% of Minnesota's population live in the Twin Cities area, but the availability of health care services is not the significant problem.

There is a high physician-population ratio, higher than the national average of areas comparable in size—1/763 (metropolitan) as compared to 1/822 (national).

Certificate of need planning has shown that there are more than sufficient hospital beds in the metropolitan area and the occupancy rates are running at a low 70-75%.

In Minnesota there are currently more Health Maintenance Organizations in operation than in any other state in the country with the exception of California.

Some of the apparent problems are transportation, cultural barriers and distribution of resources. Physicians are working on these problems with other community groups.

Manpower shortages have been a problem for a number of years. Many factors have contributed to the shortages. But concerted efforts have been and are currently being undertaken to alleviate this problem. There is always a lag in developing students to meet shortages, but in ten years, the number of students enrolled in medical school has doubled. This year there are 239 first year students at Minneapolis, 40 at Rochester and 36 at Duluth, and a total of 1,066 students overall. In the last three years, 124 senior medical students have participated in the Rural Physician Associate Program. Minnesota has the largest number of residents in family practice anywhere. Currently there are 155 and the program goal is for 180 residents.

In addition, there are various programs being developed in the state for new allied health manpower and an on-going evaluation of roles and responsibilities for a wide variety of health personnel.

In some rural areas, efforts are underway in an attempt to alleviate the problem of physician shortages. A new and unprecedented program is being implemented to produce family physicians for rural areas. Between 20 and 30 communities are involved in the Rural Physician Associate Program where senior medical students spend an academic year with local practitioners. The local physician takes full responsibility for tutoring and for the care given by the student. Over one-quarter million teaching hours and $750,000 in salaries have been provided by rural physicians thus far. While long-range results are not yet available, the expectation is that this program will be an effective approach to reducing rural physician shortages.

Availability of care in other rural areas may mean the use of emergency vehicles, helicopters, long-range diagnosis by two-way television, and other innovative programs which require the cooperative efforts of many resources. Legislative leadership in developing financial support for these kinds of programs is and will continue to be welcome.

2. In this time of rapidly rising inflation, reasonable costs for health services become increasingly important. But what constitutes reasonable cost and who is in the best position to make those determinations? Here in Minnesota we are fortunate to have developed one of the earliest physician peer review organizations in the United States. The Foundation for Health Care Evaluation has an outstanding record, and while their experience has been in the seven-county metropolitan area, they are expanding and their results can be utilized for the benefit of the entire state.

The Foundation has developed a community-wide set of prevailing fee guidelines reflecting a range of charges for the most frequent procedures. While each physician is free to set his own rates, most have been willing to adjust their fees to the Foundation's guidelines. Since 1970, the general rate of escalation in the Twin Cities area has

been 50% below the rate of escalation in physician's fees in the nation as a whole. This has resulted in several million dollars of savings to our residents. Specifically, in the last three years, physician fees have increased only 14% as compared with a cost of living increase of over 30%. The Foundation has also been involved in reviewing hospital utilization which has shown a decrease ranging from 1 and 1/2 days to 3/10 days in spite of high bed availability.

The importance of this program is two-fold. First it is having an impact on the cost of health care services and secondly, it is a voluntary program. The Medical Association strongly believes that these voluntary principles can be applied to other sectors of the health care system to effectively control costs in a way which compliments our enterprise system.

The voluntary system of peer review, as contrasted with the regulatory system proposed in the Act, involves those resources with expertise and experience and who can provide valuable insight into the problems of the system. Health care is not a public utility to be regulated solely on the basis of economic considerations. We do not think that the Senate Health Subcommittee wants health care to be equated with the electricity or water supplied to their communities, as they try to strengthen health services in the state. We feel that the delivery of quality health care can be strengthened by utilizing the voluntary approach to peer review which has proved to be an effective solution for cost control.

3. As utilization experience changes, the health care facilities should be prepared to adapt their resources to meet new and different needs in the community. We already have evidence of institutions in our cities reaching out to the community with programs like putting nurses in senior citizen hi-rises, establishing outreach programs and community clinics, developing day care centers and meal-on-wheels programs. But broad-based facilities programs designed to meet population needs should be based on facts and not assumptions. There should be provisions for identifying real needs. A proliferation of different groups doing the same thing should be avoided and a more equal distribution of services achieved. Local resources involving both providers and consumers are in a better position to determine needs and responsibility for those needs than a state policy group.
4. There are already mechanisms in this state operating to assure that duplicative institutional facilities and services are minimized. Certain technical amendments may be necessary to make the process more efficient and less cumbersome, however it would seem more appropriate to modify the existing structure than to replace it with a radically different and untested system.

Instead of conserving the limited resources in this state, the provisions outlined in this Comprehensive Health Care Act may actually serve to diminish those resources by creating a climate unattractive to potential health practitioners. Regulations by a politically appointed board could ultimately interfere wi.h the way in which a physician takes care of his patient and adversely affect the quality of care. Provisions in the act which would impose authority over innovative practice and financial agreements between facilities and practitioners could affect such highly regarded institutions as Mayo Clinic and moreover. stifle the development of "Health Maintenance Organizations." Our state could spend millions of dollars to educate physicians who will choose to practice in other states. The outstanding reputation that Minnesota has in the health care field may be seriously reversed.

5. Whenever problems develop in delivery systems in our country, government seems to respond by developing another layer of organizational structure to attack the problems, usually at considerable increase in cost and duplication of existing programs. The Minnesota State Medical Association urges the state legislature to avoid that approach here in Minnesota. There is need for more coordination between state agencies, but we believe this is better accomplished through effective inter-agency cooperation than through the development of a new policy board. A new state board takes new people, new program orientation and considerable time to develop the expertise necessary to make the important determinations outlined in this Act. In the process, the quality of health care in our state may be seriously affected.
6. The Comprehensive Health Care Act of 1975 appears to imply that all current health systems in Minnesota are not right and that

there is irresponsible operation of health care facilities. There is overwhelming evidence to demonstrate the high regard that other parts of the country have for the quality of care that is offered in this state. This presentation has suggested just some of of the programs and activities which have prompted this respect. Additionally, over 60% of the care provided by the Mayo Clinic is for patients that come from other states for care in Minnesota. There is not a single proprietary hospital in Minnesota and many of the nursing homes are run with boards of directors of interested citizens drawn from the community. Most health providers in Minnesota are committed to the continued improvement of health care delivery for our residents.

The new and innovative programs aimed at minimizing health care deficiencies in our area have been generated in a system which is balanced in responsibility and which involves those people most intimately involved in and most knowledgeable about health care—the provider. Even H.R. 16204 currently pending before the United States Congress recognizes the importance of provider participation.

> "(5) Since the health care provider is one of the most important participants in any health care delivery system, health policy must address the legitimate needs and concerns of the provider if it is to achieve meaningful results; and thus, it is imperative that the provider be encouraged to play an active role in developing health policy at all levels." (Section on Findings)

By contrast, the Comprehensive Health Care Act brings virtually every facet of health care delivery within the province of a state operated lay-controlled board. In our opinion, this would be very detrimental to the quality of health care in our state.

We feel that the above issues suggest a careful reconsideration of the way in which our health care system would be restructured if this legislative proposal were enacted.

The M.S.M.A. proposes that any modification of the health care system in Minnesota maximize the continued development of the strong aspects of our current system without additional confining governmental controls and regulations. Our suggestions include:

1. strengthening the local or county responsibility for planning and review through increased involvement of experienced physicians and other provider representatives,
2. expanding the voluntary review mechanisms, like the Foundation for Health Care Evaluation, throughout the state to cover other provider groups.
3. providing strong impetus for state inter-agency coordination which utilizes the experience of existing agencies and staffs,
4. preserving flexibility in the delivery system of health care, and permitting experimentation and innovation so as to best serve the local community need and,
5. implementing pilot projects in need areas, subject to proper evaluation, before jeopardizing current high standards of medical care through an untried and unproven statewide system.

In developing approaches to the identifiable problems in our state, the Minnesota State Medical Association strongly feels the implementation of regulatory agencies and controls that with lack of experience, threaten the quality of care, access to care and total cost of care should certainly be avoided.

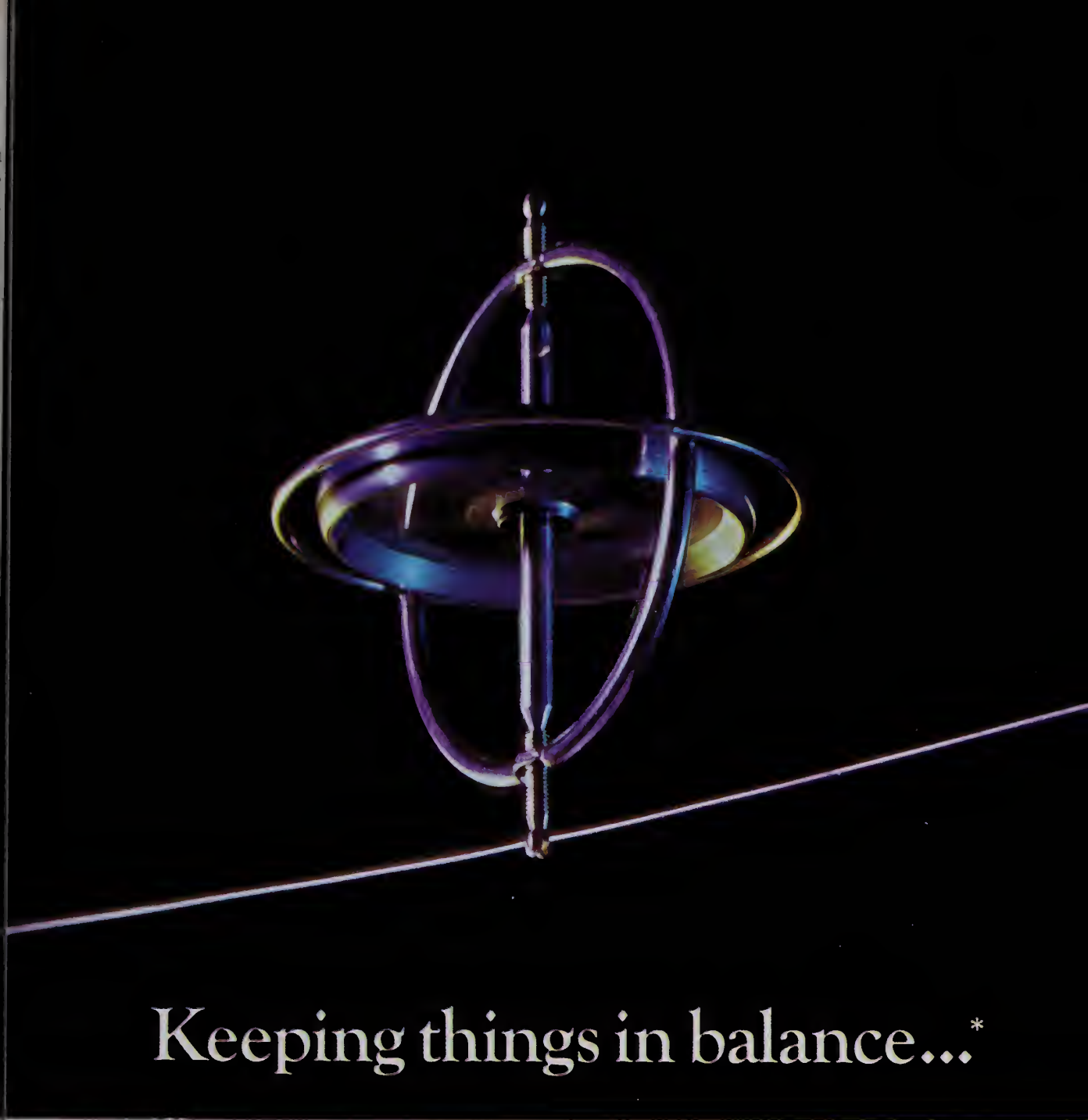
We further stress to the legislature that at no time should costs be the controlling factor in determining the quality of health care.

Physicians in our state stand ready to work with the legislature in developing adequate data on health needs and in determining appropriate and effective mechanisms for utilizing the experience of comprehensive health planning and peer review in an approach to solving some of our health service problems.

With a joint private sector/government partnership with balanced input from both, we can determine where the areas of need lie and can assure the continued development of high quality health care in Minnesota.

Annual Meeting

The Minnesota State Medical Association's Annual meeting in St. Paul, May 21-23, 1975, at the St. Paul Hilton Hotel.



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*INDICATIONS. Based on a review of this drug by the National Academy of Sciences-National Research Council and/or other information, FDA has classified the indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

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The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy. See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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Atlantic City

(Continued from page 94)

BIOLOGICAL RHYTHMS IN HUMAN AND ANIMAL PHYSIOLOGY. By Gay Gaer Luce, Dover Publications, Inc., New York, N.Y. 183 pp. Paper back. Price $2.50.

At first impulse most clinicians would consider a dissertation on biological rhythms no more than a sterile and abstract discipline.

Yet, those of us who have frequent contact with endocrine disorders, such as diabetes mellitus, have become aware of a circadian rhythmicity in blood glucose levels and insulin requirement, which is constant for a given individual but changes from patient to patient.

The circadian rhythms of body temperatures are known to every clinician, as is the temperature variation of the menstrual cycle.

The extensive review by Gay Gaer places the impact of circadian and other rhythms in focus and emphasizes the questions asked by Dr. Franz Halberg of Minnesota and other investigators around the world:

How much do we learn from chemical and hematological laboratory tests, which are performed at variable hours of the day?

Does a given medication have the same effect, when administered at different times of the day?

Is a toxic drug more or less toxic at certain times of the day?

Chronobiologists, particularly Dr. Halberg's group, have precise information to many of these problems. Since most, if not all cellular functions are subject to circadian rhythms, any substance administered to an individual will be metabolized more effectively at the peak activity of the cell and least at its rest period. The rhythms for various organs are by no means synchronized. As a matter of fact, certain cell groups within an organ may have different rhythms, such as the α and β cells of the pancreas.

The problem becomes most intriguing and of consuming clinical interest where it involves malignant proliferaton of cells. Present day therapy is detrimental to malignant cells as it is to their normal counterparts. Malignant cells have been found to have a subdued or different rhythm from non-malignant ones. Therapy at a time when the normal cells are at their lowest metabolic rate should result in minimal toxicity whereas at that time it may be effective for their malignant counterpart. Indeed, Dr. Halberg and associates have demonstrated this to be the case in murine leukemia.

This monograph is a stimulating challenge to the serious clinician as well as to the investigator. It is well written and well organized in text and bibliography.

Horace H. Zinneman, M.D.
Veterans Hospital

MANUAL OF ROUTINE ORDERS FOR MEDICAL AND SURGICAL EMERGENCIES, Timothy A. Lamphier, M.D., F.A.C.S.: Von Mizell, M.D.; Robert Mayer, M.D. Warren H. Green, Inc., St. Louis, Missouri.

In considering the emergent treatment of any medical or surgical problem, the thought of "Routine Orders" almost makes one shudder with apprehension.

In order to simplify the care of a patient, as well as to avoid the hazard of overlooking something, the learning of many things by rote is an advantage. From that perspective the extensive lists of routine orders for the various emergencies constitute an excellent reference from which orders for the care of a patient can be selected.

I can readily understand that this Manual at every nurse's station would be an asset. No doubt it would be well-worn by the hands of interns, residents, nurses, and attending staff, who would be happy to check with the extensive lists, of the emergent orders to be considered, as described in this Manual.

There is no index, but the Table of Contents identifies the location of each body system and its most common emergent problems.

There are 124 pages, a dozen or so of unnumbered diagrammatic pen-and-ink drawings of, principally, the upper and lower respiratory system, and one illustration for the Rule of Nines in describing the percentage of burn.

Carl O. Rice, M.D., Ph.D.
Editor-Emeritus

CURRENT PEDIATRIC DIAGNOSIS AND TREATMENT; C. Henry Kempe, Henry K. Silver, and Donaugh O'Brien. Third Edition, Lange Medical Publications, Los Altos, California. Price: $12.00.

This volume continues to be a good general quick reference book for the student and practitioner in pediatrics.

Reorganization of material is found in the sections on neonotology, nutrition, ambulatory pediatrics, ENT, the respiratory tract, cardiology and hereditary disorders.

In some instances, new information is added. While these changes are consistent with the high editorial quality maintained by the authors, the change will hardly justify purchase of this third edition by owners of the second editions in usable condition.

Martha Burke Strickland, M.D.
Uvalde, Texas

BLACKS AND AMERICAN MEDICAL CARE—Max Seham, M.D., University of Minnesota Press, Minneapolis, Minn. 1973. 116 pages. $7.95.

This is an escape into reality. In a world where physicians stumble wearily home from laboring in the vineyard to be confronted by sour grapes, innuendos and accusations by the press, it is almost a pleasure to be taken to task by a well-informed peer.

Dr. Seham has refrained from engaging in impassioned rhetoric and has produced a book of brevity and clarity. While one can argue the validity of statistics as only historical, their wide use in this volume documents the injustices which the author's wide experience confirms.

Any vague uneasy feeling that injustice has been done is laid out clearly in black and white; an informed base is provided from which progress can be made toward equality. Past discrimination in the care of the poor; racial prejudice in education and medical schools; the past and present acceptance of the black physician and the hopes and aspirations for the future are thoroughly presented. Whether, as the author pleads, Federal intervention can hasten that progress is something we can only wait and see.

Theodore H. Sweetser, Jr., M.D.
Minneapolis, Minnesota

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Minnesota Society of Clinical Pathologists

Symposium on Endocrine Disorders

Date: Saturday, April 5, 1975

Place: Health Sciences Building, University of Minnesota

9:45-10:00 a.m.: Welcome Address and Announcements—Charles Chedister, M.D., President

10:00-11:00 a.m.: Histology of the Thyroid Gland in Normal and Abnormal States—Louis B. Woolner, M.D.

11:00-12:00 noon: Thyroid Function Testing—Colum A. Gorman, M.D.

12:00- 1:30 p.m.: Luncheon at Campus Club, Coffman Union

1:30- 2:00 p.m.: Normal and Abnormal Histology of the Parathyroid Gland—Erhard Haus, M.D.

2:00- 2:30 p.m.: Parathyroid Function Testing—Arnold Lindall, M.D., Ph.D.

2:30- 3:15 p.m.: Adrenal Gland Function in Normal and Abnormal States—Richard Doe, M.D.

3:15- 3:45 p.m.: Histology of the Adrenal Gland in Normal and Abnormal States—J. Aiden Carney, M.D.

4:15- 5:00 p.m.: Endocrine Aspects of Hypertension—David M. Brown, M.D.

7:30 p.m.: Commemorate E. T. Bell Banquet for friends of Dr. Bell and members of the Society, Marquette Inn

Tuition: $10.00 (includes luncheon, lecture summaries, and booklet of 35 mm. slides; dinner additional)

Applications: Before March 15 to: Wayne A. Chadbourn, M.D., Secretary, Minnesota Society of Clinical Pathologists, 900 South 8th Street, Minneapolis, Minnesota 55404

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Precautions:

ORAL: In the elderly and debilitated and in ildren over six, limit to smallest effective sage (initially 10 mg or less per day) to clude ataxia or oversedation, increasing adually as needed and tolerated. Not recom- ended in children under six.

INJECTABLE: Keep patients under observa- n, preferably in bed, up to three hours after tial injection; forbid ambulatory patients to erate vehicle following injection; do not minister to patients in shock or comatose tes; use reduced dosage (usually 25 to 50 g) for the elderly or debilitated and for ildren age twelve or older.

ORAL AND INJECTABLE: Though generally t recommended, if combination therapy th other psychotropics seems indicated, refully consider individual pharmacologic fects, particularly in use of potentiating mpounds such as MAO inhibitors and enothiazines. Observe usual precautions in esence of impaired renal or hepatic func- n. Paradoxical reactions (e.g., excitement, mulation and acute rage) have been ported in psychiatric patients and hyper- tive aggressive children. Employ usual



precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

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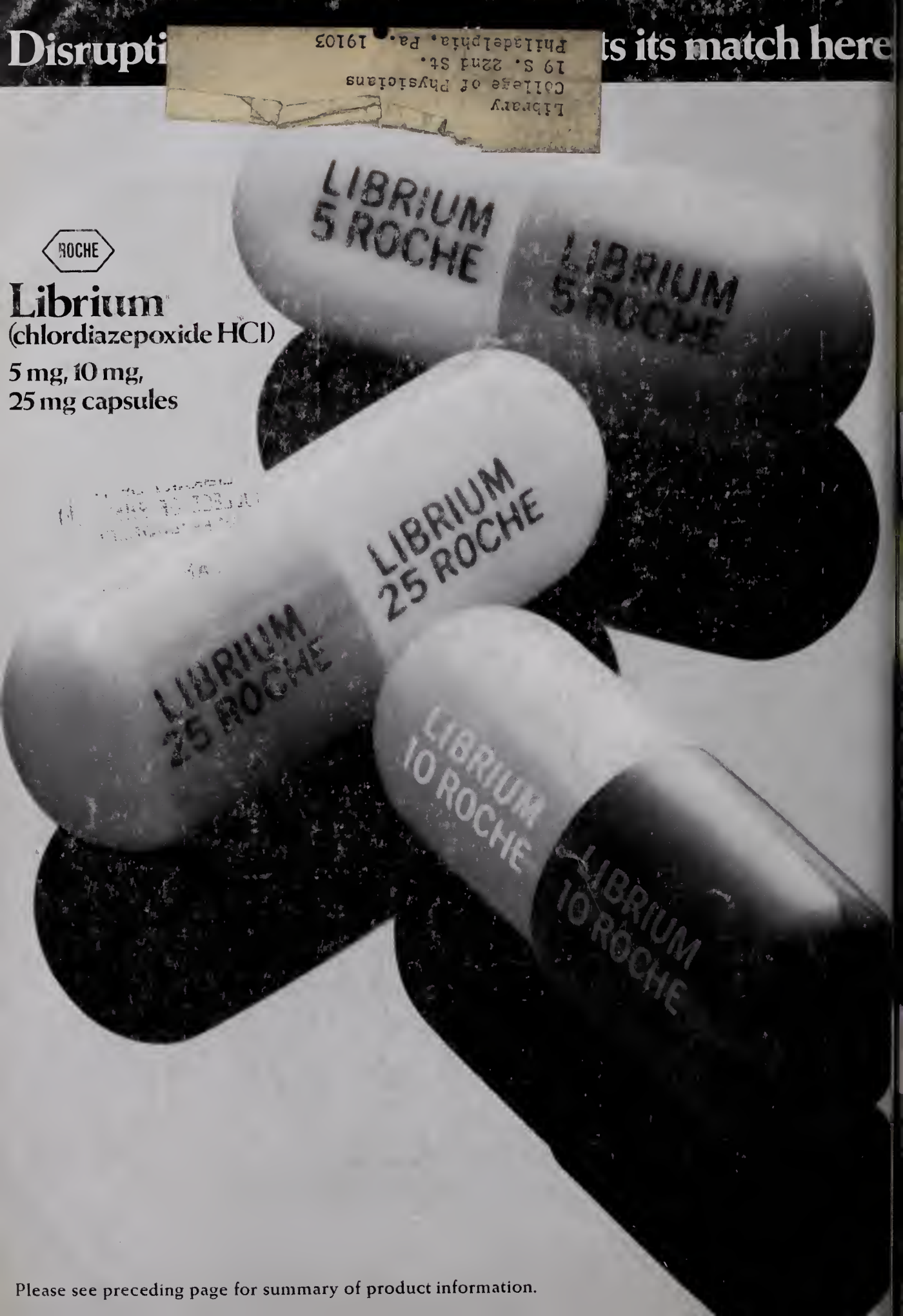
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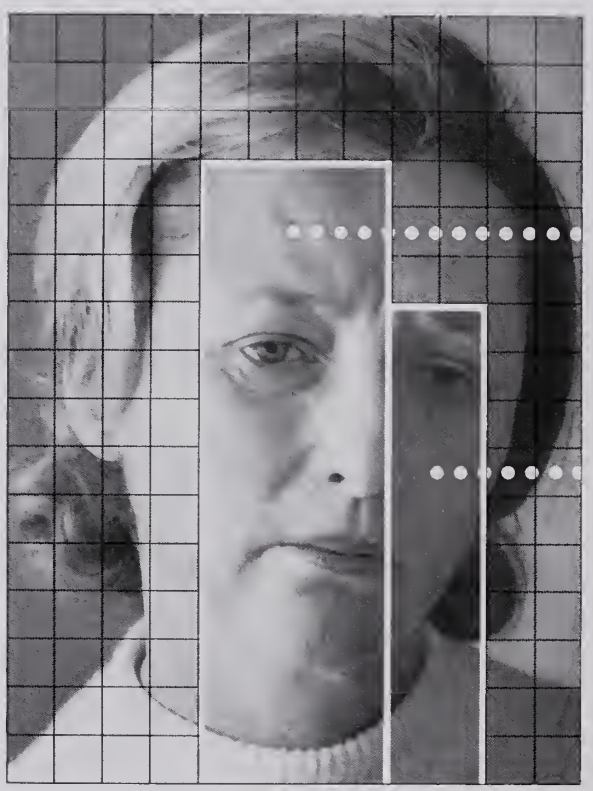


Hugh J. Williams, M.D.

FEBRUARY, 1975

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in f and/or severity of grand mal seiz require increased dosage of stanc convulsant medication; abrupt wi may be associated with temporar crease in frequency and/or sever seizures. Advise against simultan gestion of alcohol and other CNS sants. Withdrawal symptoms (sin those with barbiturates and alcoh occurred following abrupt discon (convulsions, tremor, abdominal cle cramps, vomiting and sweatir addiction-prone individuals unde

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Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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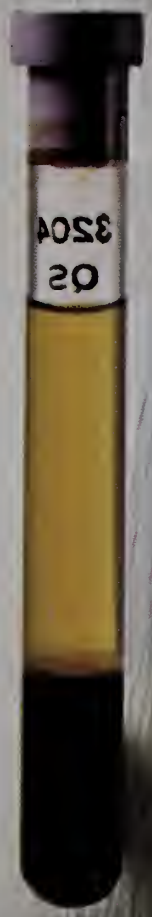
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See prescribing information in package insert reproduced below.

	Starting Dosage	Increased Monthly by	Usual Maintenance	Maximal Recommende
Adult Hypercholesterolemic	1.0-2.0 mg.	1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac	0.5-1.0 mg.	1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as D-3,5,3′,5′-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre, subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

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President's Letter

From the Patient's Point of View

WE AS PHYSICIANS are continually asked to evaluate and review the professional qualifications of our colleagues. For this purpose we have established detailed standards of care and treatment. However, have we ever considered the physician's qualifications from the patient's point of view? What attitudes does the patient treasure in his or her doctor?

It seems as one talks to patients that they assume their physicians have proper medical training and knowledge. The doctor's expertise is accepted without question. What sets him apart are human qualities. Patients need to know that their doctors care. Most people, if only subconsciously, want to be sure that if they get a sharp pain in the abdomen, or even a mild pain in the neck, the doctor will not suggest through an appointment secretary that he is unable to take any appointments for two weeks. A patient wants to feel that his doctor will be available when he needs him.

To us, availability may seem a demanding chore. But it is not impossible. The doctor must be available, not only at the office or hospital, but by telephone or through conscientious assistants who must always speak to patients with courtesy, warmth, and understanding. Through a well planned and responsible coverage arrangement, we can be, in effect, always available. The best trained and most capable physician can not fulfill his calling if he insulates himself from his patients and is only available at his pleasure.

Patients also say that when the doctor is available, he must also be approachable. He must make them feel that any question is significant, even though he may have answered it many times already. He must talk with them as intelligent persons capable of understanding the nature of their disease, condition, and prognosis.

If we expand a little on the matters of availability and approachability, we come naturally to the matter of concern. Patients want their physicians to be concerned for them as individuals. It seems to me that the most healing medicine a physician can give is for him to truly care. He must take the time to listen and to remember—review the chart before seeing the patient—what the problem is. Through words, gestures, the eyes, and the smile, the sincere physician shows his true concern.

Concern should not only include the patient's health, but should encompass many other things. The physician should consider the monetary cost inflicted upon the patient as well as the attitudes of the patient's family toward the illness. He must be concerned that his directions are understood and accurately carried out.

Dr. Karl Wilhelm Stenstrom, to whom this issue is dedicated, exemplified the concern and caring that patients always need. Dealing almost entirely with patients suffering from malignant disease, he urged all physicians in training to know and to understand the patient's problems. He continually stressed review of treatment results in order to modify and improve care. His concern was for the welfare of his patients.

Many of the criticisms and problems besetting medicine arise from the increasingly impersonal nature of the physician-patient relationship. Perhaps it is time we return to the basics of our calling. Perhaps it is time we heed the patient's point of view, and apply a good dose of old-fashioned care and concern to our medical practice.

Bernard Hall M.D.

President
Minnesota State Medical Association

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Editor's Notebook

Preface

I shall say a word about this issue and the life of a former member of the Board of Editors.

This issue contains papers on the Art and Science of Radiology and Nuclear Medicine. You will not find these papers easy to read, for many describe recent technological advances. But you will discover new knowledge you would not ordinarily run across in a general medical journal like MINNESOTA MEDICINE. *Despite the rough mental sledding, I am sure you will learn something practical and worthwhile—as I have.*

I commend Dr. Shih Tsai of Hennepin County General Hospital who gathered together the radiological articles and Dr. Merle Loken of the University of Minnesota who recruited the authors for the nuclear medicine paper.

Harold Jacob Strickler, M.D. (January 10, 1915-January 4, 1975)

"Man's chief purpose is to live,
not to exist.
I shall not waste my time trying to prolong them.
I shall use my time."—Jack London

I knew Jake Strickler for nine years as a surgeon and for six years as a member of the Board of Editors of MINNESOTA MEDICINE. This was too short a time to know him intimately, but long enough to know him well. Long enough, too, to know his energy and enthusiasm were always bubbling over, often in unexpected ways. Jake, for example, didn't walk: he dashed through the hospital corridors with arms flapping. For he was a man in a hurry, intent on doing something with every moment he had.

Jake would appreciate the Jack London quote: London was his kind of man—vigorous, courageous, self-reliant, adventurous, and defiant in the face of adversity. Besides, Jack London was an Arctic man. Jake often read about Arctic explorers. Maybe this reading, or his Brainerd boyhood, had something to do with his preference for cold weather. Cold seemed to get his juices boiling, to heighten his sense of challenge.

Whatever drove him, Jake lived vigorously. The busier his practice; the more determined he was. The tougher the operation; the more intense he became. The more adverse the conditions, including serious illnesses that plagued him his last 14 years, the more he plunged into what he enjoyed.

He often waterskied just as the Spring ice broke up; twice journeyed above the Arctic Circle and canoed more than 500 miles through the Canadian wilderness, once shortly after major surgery; went by rail with his wife, Helen, to Hudson Bay in January to soak up the cold and to warm his soul; sailed across an open stretch of Carribean without benefit of previous oceangoing navigational experience; scubadived in the frigid depths of Lake Superior to search for hulks of old ships; conducted an unofficial but well known waterskiing school for the uninitiated on the waters of Lake Minnetonka; and carried on a full surgical practice that culminated in his becoming Chief of the St. Barnabas Hospital Medical staff and President of the Minnesota Surgical Society. Somewhere along the line, he sandwiched in 40 contributions to medical journals.

Jake's family—his wife, Helen, and his sons, Jeff and John—participated in many of these activities. They shared and inherited his zest and vigor. To his sons he transmitted his love for Medicine. Jeff is now a pediatrician, and John, a premedical student.

Many of his surgical colleagues will remember him for his courageous fight against the practice of fee splitting. He fought for this principle in the mid fifties, weathered the ensuing storms, and saw the climate of surgical practice improve in the sixties. In his own practice, he was affiliated with Doctor Carl Rice and Doctor William Heupel.

He used his time well. I shall miss him.

Richard L Reece MD



KARL WILHELM STENSTROM, Ph.D.
1891-1973

Dr. Karl Wilhelm Stenstrom, former Professor of Biophysics and Director of the Division of Radiation Therapy at the University of Minnesota Hospitals, died at his home in Holmes Beach, Fla. on Nov. 7, 1973 after a brief illness. Dr. Stenstrom was born in Gothenberg, Sweden on Jan. 28, 1891 and was in his formative years in Sweden when Xrays and radioactivity were discovered. These discoveries gave birth to the science of radiation medicine, to which Stenstrom devoted his professional life.

After earning his doctorate in physics at the University of Lund, Stenstrom received a fellowship to study at Harvard University. A year later he moved to the State Institute for the Study of Malignant Disease in Buffalo, N.Y. (now Roswell Park Memorial Hospital), where, in 1921, he standardized the first 200 kV x-ray machine built by General Electric for use in radiation therapy. He continued his work in Buffalo with Dr. H. Holfelder, a physician trained at the University of Frankfurt, performing treatment of patients with this new machine. It was at this time that he met and married Annette Treble, a young physician in training at the Institute. Dr. Stenstrom joined the Radiological Society of North America in 1925.

In 1926, a Cancer Institute was established at the University of Minnesota and Stenstrom was invited to supervise the standardization of x-ray equipment and radium to be used for the treatment of patients. A short time later he was made Director of Radiation Therapy, a position he held until his retirement in 1956. Radiation therapy developed rapidly at the University of Minnesota under Stenstrom's leadership, and during his tenure more than 30,000 cancer patients were treated. He used 200 kV radiation for therapy until a 400 kV unit was installed in the early 1940's. In 1953 a cobalt teletherapy unit was installed for cancer therapy (the second unit of its type to be installed in the United States). Dr. Stenstrom introduced the use of radioisotopes for diagnostic and therapeutic purposes, thereby laying the foundation for nuclear medicine.

Dr. Stenstrom published more than 100 scientific articles, many of which represent significant "firsts." These articles relate to radiation physics, radiation biology, radiation therapy, physical therapy, and nuclear medicine. Other works include *Roentgen Spektra* (1919) and *Manual of Radiation Therapy* (1956).

In 1948 the Order of the North Star was conferred upon him by the Swedish Crown for his scientific and cultural contributions. In 1958 he received the American Cancer Society Award for distinguished service in the control of cancer, and in 1968 he was included in the *World's Who's Who in Science.*

Dr. Stenstrom is survived by his wife Annette, a daughter (Mrs. A. M. Richards), and three grandchildren.

A memorial fund in Dr. Stenstrom's name has been set up by the Minnesota Medical Foundation at the University of Minnesota. The fund will be used to establish the Stenstrom Lectureship, which will be presented annually on some aspect of radiation medicine.

Merle K. Loken, M.D., Ph.D.

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References: 1. Reuter, S.H., and Montgome W.W.: Arch. Otolaryng. *80*:214-217 (Aug.) 19 **2.** Osol, A., et al., ed.: The United States Dispensatory and Physicians' Pharmacolog ed. 26, Philadelphia, J.B. Lippincott Co., 19 p. 171. **3.** Schwartz, A.D., and Pearson, H.A. J. Pediat. *78*:558-560 (March) 1971.

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Minnesota Radiological Society

Reflections on a Physicist Turned Clinician

IT IS GIVEN to few men to be true pioneers. Timing and appropriate preparation may be fortuitous, but the dedication, foresight, and steadfast application of the pioneer must be supplied by the man himself. Such a pioneer was Karl Wilhelm Stenstrom to whom this issue of MINNESOTA MEDICINE is affectionately dedicated.

Engaged as a young physicist to supervise the installation of the first radiation therapy equipment at the University of Minnesota in 1926, Dr. Stenstrom stayed to pioneer its use. He lived to introduce another clinical branch at Minnesota in the post-Manhattan Project era: nuclear medicine. His physicist's training lent a methodical, mathematical approach to his work and added a refreshingly objective dimension to the man he eventually became: a great clinical oncologist.

"Stennie," as he was known to colleagues, residents, and students alike, was a gentle, shy and thoughtful man, moving softly among towering egos. He must have sensed a private satisfaction as they strained at tumor conferences to catch the ideas expressed in his quiet Scandinavian accent. For they knew that here was an authentic source on cancer management, an authority self-taught by years of careful observation, meticulous follow-up, and a mathematician's expertise at statistical method.

A perpetual searcher, Dr. Stenstrom refined physical methods of radiation measurement at a time when others were still speaking in biologic terms of "erythema doses." He lectured on the tumor-host relationship long before it became fashionable to link immunology and oncology. With his characteristic moderation in radiation dosage he seemed to have discovered for himself the Hippocratic injunction, "above all do no harm."

"Stennie" would have smiled at the current concern over recertification of physicians. As a pioneer and a life-long outsider he would have wondered how one recertifies a man who had never been certified in the first place. But he was also a realist who recognized that all do not share his own intense motivation. He probably would have approved the idea.

Warren L. Kump, M.D., President
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Office Radiology for the Non-Radiologist

C. W. FRYE, M.D.*

Satisfactory x-ray examinations can be done in the private office if certain limitations are recognized. These include technical limitations of equipment, the ability of the technologist and the experience and training of the physician in charge.

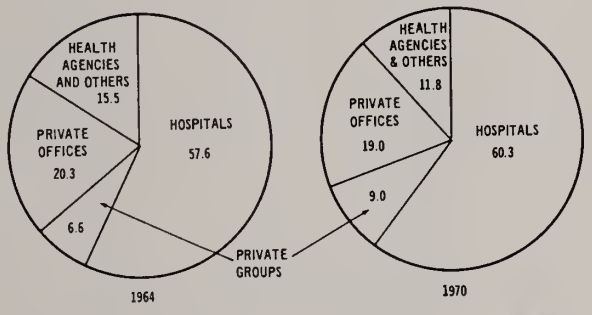
FOR THE PAST FEW years there has been an increasing awareness of environment, heredity and possible adverse effects from many things which were once unquestioned. Medical x-ray exposure is one of the former "sacred cows" which is receiving scrutiny. It is appropriate to review indications, procedures and equipment to assure ourselves that our patients receive maximum benefit from each x-ray exposure.

Until recently it was felt that low dose exposure to radiation had no adverse effect. We know now that this is not necessarily true. An increased incidence of leukemia has been shown to occur in individuals who were exposed to radiation before birth.[1,2] The association of thyroid neoplasms and low dosage head, neck and mediastinal radiation in children has been established beyond question.[3,4] Certainly, genetic damage can and does occur with small exposures to radiation. At the present time there has not been a measurable increase in the number of birth defects which can be traced to diagnostic x-ray exposure. Genetic damage, however, is permanent, cumulative and inherited so we must limit genetic exposure now to avoid setting a genetic time bomb which will affect future generations.

While one might think that the problem of radiation exposure is primarily concerned with hospitals, United States Public Health Service statistics indicate that more than 25% of all x-ray exposures are made in private offices and group practices (Table 1). Furthermore, this percentage is increasing. Data from this same source also indicates that the patient exposure for each examination is likely to be higher in the private

TABLE 1

ESTIMATED PERCENT DISTRIBUTION OF MEDICAL X-RAY PROCEDURES by Type of Facility, U.S., 1964 and 1970

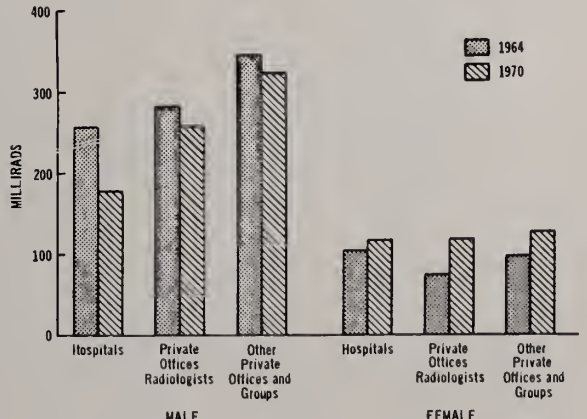


PHS X-ray Exposure Study
Preliminary Data

September 1971
Figure 25

TABLE 2

MEAN GONAD DOSE ESTIMATES FOR ABDOMINAL RADIOGRAPHS by Type of Facility and Sex U.S., 1964 and 1970



PHS X-ray Exposure Study
Preliminary Data

March 1972

*St. Paul, Minnesota.

office than in the hospital or in the radiologist's office (Table 2). This being true, then any attempt to limit the general population exposure to Xrays must certainly include the private office and this brief paper is directed primarily to the office practice of radiology.

For our purposes we can consider that an x-ray examination involves three processes. First is indication or patient selection. Second is the conduction of the examination and this may be further broken down into the technologist and mechanical factors. Third and finally is interpretation of the completed examination. Before considering these factors separately we should give some thought to the relationships of the factors. It should be noted that the diagnostic value of an examination is not decided by averaging the above factors, but is limited to the level of lowest proficiency. Strength in one area cannot compensate for weakness elsewhere. The finest equipment cannot produce satisfactory results if the technologist is incompetent. Good equipment and a well trained technologist are of no value if the interpreter has neither the knowledge, experience nor time to extract the information from the films. Certainly any examination ordered without medical indication has no diagnostic value even though the examination is skillfully done and carefully interpreted. This concept is important because any attempt to upgrade an x-ray operation must concentrate on the "weakest link." Purchase of a new x-ray machine or the hiring of a different technologist will produce disappointing results if the actual limitation is elsewhere.

It is beyond the scope of this paper to discuss indications for x-ray examination in any detail.

TABLE 3
Radiation received by the gonads*

Examination	Techniques kv	Techniques ma-sec	Target-film distance (in.)	Films per examination	Exposure dose per film Male (mR)	Exposure dose per film Female (mR)
Skull	65	125	36	4	0.2	0.05
Sinuses	80	100	30	4	0.2	0.05
Mastoid	70	100	30	4	0.2	0.05
Teeth						
Whole mouth	65	10	8	14	0.34	0.06
Bitewing	65	40	8	1	0.34	0.06
Others	65	10	8	1	0.34	0.06
Chest						
Straight	68	AT†	72	1	0.36	0.07
MM‡	83	24	36	1	0.25	0.15
Tomograph	62	50	48	6	6.2	0.9
Ribs, anteroposterior	65	100	36	1	0.48	0.16
Shoulder, anteroposterior	58	50	36	1	0.22	0.03
Spines						
Cervical						
Anteroposterior	58	100	36	1	0.27	0.06
Lateral	70	150	60	2	0.92	0.20
Dorsal						
Anteroposterior	62	200	36	1	8	11
Lateral	68	200	36	1	13	2.1
Lumbar						
Anteroposterior	68	200	36	1	24	227
Lateral	72	500	36	1	26.6	86
Anteroposterior	120	20	36	1	6	40
Lateral	120	60	36	1	7	16
Lumbosacral joint						
Anteroposterior	80	300	36	1	22	220
Lateral	120	350	36	1	15	800
Sacroiliac joint, anteroposterior	63	200	36	1	57	180
Pelvis, anteroposterior	65	100	36	1	1100	210
Hips, anteroposterior	68	200	36	1	710	210
Abdomen, anteroposterior	72	100	36	1	69	200
Intravenous pyelography, renal	72	100	36	3	69	200
Intravenous pyelography, bladder	72	100	36	3	93	230
Gallbladder, posteroanterior	70	150	36	3	0.6	5.2
Abdomen, obstetrics	80	150	36	1	—	260
Pelvimetry						
Oblique, anteroposterior	120	200	36	1	—	240
Lateral	120	100	36	1	—	840
Fingers, wrist, and elbow	58	25	36	2	0.13	0.026
Knee, tibia, and fibula	67	50	36	2	3	0.55
Foot and ankle	62	25	36	2	0.62	0.012
Barium meal	70	360	24		20	9
Barium enema	70	360	30		40	20

*Based on data from Stanford, R. W., and Vance J.: Brit. J. Radiol. 28:266-273, 1955; from Braestrup, C. B., and Wyckoff, H. O.: Radiation protection, Springfield, Ill., 1958, Charles C Thomas, Publisher.
†Automatic timing.
‡Photofluorography.
Chart adopted from: Merrill, Vinita: Atlas of Roentgenographic Positions, Vol. I, 3rd ed., C. V. Mosby, St. Louis, 1967. By permission.

It is in this area of decision that the greatest potential for reduction of radiation exposure exists. Obviously, if it is decided that an x-ray is not needed, then there is no exposure and the reduction is 100%. Any examination done must, of necessity, involve some exposure to radiation. One should consciously weigh expected benefit against hazard with every examination ordered. It is especially important to limit exposure for persons below the age of 40 since this age group is the reproducing population. A single ionizing event or "hit" on a gene can produce permanent damage and it is clear that any x-ray exposure carries some risk. Examinations such as abdomen, pelvis and lumbar spine result in rather large gonadal doses.

Table 3 shows gonadal exposure from some of the frequently ordered examinations.

The non-medical indications may be the most difficult to control. In this category are examinations done at the request of the patient and without medical justification, as well as films requested by lawyers and insurance carriers. Any examination made purely for documentation represents excess radiation exposure to the patient. Other types of examination which can often be eliminated are the mass survey and yearly routines in asymptomatic individuals. These are not productive and should only be done on individuals or groups whose work or personal habits expose them to conditions known to be hazardous.

Once the decision has been made that an x-ray examination is indicated, the technologist assumes responsibility for the conduction of the examination. At the present time there is no legal requirement detailing the qualifications of an x-ray technologist and anyone may operate a machine under the direction of a physician. There are several national registry programs for x-ray technologists and these are based on examination. Registration may indicate but certainly does not guarantee competence. Two simple tests may be applied to judge the performance of the technologist. The first of these is the quality of the finished examination. It should be properly positioned, exposed and developed with no artifacts to confuse the interpretation. The second test is the number of re-takes required to produce a good final product. Frequent reexaminations due to faulty technique cannot be tolerated as each such failure represents excess radiation to the patient. In order to help the technologist every department should include at least one of the standard references on positioning. The physician should insist that the technologist develop and use a technique chart based on actual measurement of the patient. In the final analysis, the physician in charge must assume responsibility for the performance of the technologist and must not tolerate mediocrity for the sake of expediency.

X-ray machines come in a wide variety of sizes, colors and models much the same as the American automobile. They also have a wide variety of power or output. The less expensive machines found in many private offices tend to have low output and are not capable of doing a full range of examinations. Equipment which can produce good radiographs of extremities and possibly chests may not have sufficient output to do abdominal or spine work. The physician in charge must not request x-ray examinations beyond the capability of his machine. A few selected techniques are suggested in Tables 4, 5, 6. These can be used in the evaluation of a machine to determine which examinations should not be attempted.

Every x-ray machine is required by Minnesota State regulations to be equipped with a device to limit the size of the x-ray field. The physician in

TABLE 4

Suggested Maximum Exposure Time for Various Parts of the Body. Any longer time may result in an unsatisfactory film, (motion).

1.	Small extremities	1.0 sec.
2.	Large extremities	1.0 sec.
3.	Skull	½ sec.
4.	Sinuses	½ sec.
5.	Pelvis and AP vertebral column	1.0 sec.
6.	Abdomen	1.0 sec.
7.	Lateral vertebral column	2.0 sec.
8.	GI tract	3/10 sec.
9.	Chest, PA	1/20 sec.
10.	Chest lateral	2/10 sec.
11.	Gallbladder	½ sec.

TABLE 5

The following kilovoltages are necessary for the penetration of various parts of the body—any less may result in an unsatisfactory film.

1.	Small extremities	60- 65 kv
2.	Large extremities	75- 80 kv
3.	Skull	75- 80 kv
4.	Sinuses	70- 75 kv
5.	Pelvis & AP vertebral column	70- 75 kv
6.	Abdomen or KUB	70- 75 kv
7.	Lateral vertebral column	80- 85 kv
8.	GI tract	90-120 kv
9.	PA chest	75 kv
10.	Chest, lateral	90 kv
11.	Gallbladder	70 kv

TABLE 6
MaS to be used for various parts of the body, (approximate).

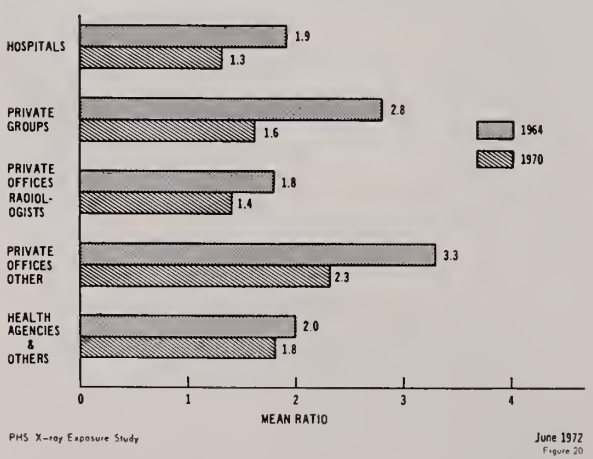
1.	Small extremities	cardboard 120 cassette, other than cast 3 MaS
2.	Large extremities	cardboard 150 MaS cassette, other than cast 5 MaS
3.	Skull	75 MaS
4.	Sinuses	75 MaS
5.	Pelvis, AP vertebral column	200 MaS
6.	Abdomen	200 MaS
7.	Lateral vertebral column	400 MaS
8.	GI tract	90 MaS
9.	Chest, PA	10 MaS
10.	Chest lateral	60 MaS
11.	Gallbladder	150 MaS

The above is used with med speed screens.

charge must insist that the collimator be used to limit the exposure field to the area of interest.* Excessive field size is one of the major factors in increasing gonadal dose above minimum values. Table 7 shows United States Public Health Service statistics on the collimation of x-ray machines. In 1970 in private offices the x-ray beam exposed an area 2.3 times larger than the film being used. In an ideally controlled situation this value should be one or slightly less. The physician should insist on seeing the limits of the collimated beam on each film to assure that proper beam restriction is being used.

TABLE 7

ESTIMATED MEAN RATIO OF BEAM AREA TO FILM AREA FOR RADIOGRAPHIC EXAMINATIONS
by Type of Facility, U.S., 1964 and 1970



There are two special situations which should be mentioned at this point. The first of these concerns fluoroscopy. About half of the office x-ray machines in Minnesota are equipped to do fluoroscopy. Many if not most use ordinary fluoroscopic screens. The state of technology today is such that fluoroscopy should not be done without some form of image intensification. The use of image intensification permits lower dose rates while increasing the information content of the examination. In addition, fluoroscopy should only be done by those specifically trained in its use. Misuse of the fluoroscope is potentially the most hazardous of diagnostic x-ray procedures.

A second practice mentioned only to condemn is that of doing a gastrointestinal examination by giving barium either by mouth or enema and filming without the use of fluoroscopy. Such examinations cannot exclude pathology, are seldom useful in confirming the presence of a lesion and therefore should never be done.

The final step in an x-ray examination is its interpretation. The competence of the physician interpreter is the most difficult evaluation that we must make. Most laymen assume that the license to practice medicine includes proficiency in all areas including x-ray diagnosis. This is not true. Medical school training in radiation physics and film interpretation ranges from none to minimal. Any expertise that the average practitioner has is the product of postgraduate education and self-teaching. As would be expected, abilities range from none to very good. Sincere self-evaluation is required. The physician using Xray in his office should not order films which he does not feel competent to interpret unless consultation is readily available. The x-ray department of any office must include several of the standard text references in x-ray diagnosis. In addition, a comfortable viewing area with several view boxes and a high intensity illuminator is needed. The examination is completed only after the films have been carefully studied and a written report produced for clinical record.

Summary

It is our goal to achieve optimal use of medical x-ray examinations so that a maximum of useful information is obtained while patient exposure is kept at minimal levels. This can be done by careful attention to the following: (1) Every examination must have sufficient indication so that either positive or negative results will have diagnostic value. (2) The examination should be conducted by a skilled technologist on an adequate machine. Standard views and positions should be used. (3) The films should be care-

*Effective August 1, 1974, HEW regulations state that any new x-ray diagnostic unit shall be equipped with an automatic collimating device.

fully studied and a written interpretation placed in the patient's record.

To do anything less than the above is to expose the patient to unnecessary radiation.

References

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2. Brit Med J i:981, 1961.
3. J Nat Cancer Inst 31:1357, 1963.
4. J Nat Cancer Inst 33:277, 1964.

Winter Retreat

Office Psychiatry for the Practicing Physician

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Saturday, February 15, 1975 — Radisson Inn-Plymouth

Morning Session
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9:00- 9:40 ..... Welcome—Unmasking a Psychiatric Problem
Question and Answer Period
9:40-10:20 ..... The Many Facets of Depression
Question and Answer Period
10:40-11:20 ..... Practical Aspects of Human Sexuality
Question and Answer Period
11:20-12:00 ..... Film—Excerpts from Great Movies—
Patient Implications
12:15 ..... Luncheon
Speaker—"Is Psychiatry Dead?"

Afternoon Session
(Conference Theatre)

1:30- 2:10 ..... The Message About Hypochondriasis
Question and Answer Period
2:10- 2:50 ..... Every Physician and Office Child Psychiatry
Question and Answer Period
3:10- 3:50 ..... Alcoholism and Abused Drugs—Early Indicators
3:50- 4:30 ..... Panel Discussion—Problem Cases
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Address inquiries to: Dorothy M. Bernstein, M.D., 1011 Medical Arts Building, Minneapolis, MN 55402.

Recent Advances in Neuroradiology

Some Aspects of Computerized Transaxial Tomography of the Head

O. WAYNE HOUSER, M.D.*; HILLIER L. BAKER, JR., M.D.*;
J. KEITH CAMPBELL, M.D.*; DAVID F. REESE, M.D.* and COLIN B. HOLMAN, M.D.*

Computerized transaxial tomography is a new method of radiologic imaging which is proving to be important in the evaluation of the patients with neurologic problems. The procedure is noninvasive, yet unique because the actual parenchyma of the brain is displayed. Currently, this display permits identification and differentiation of a wide variety of neurologic and neurosurgical disorders; however, further development may yield additional insight into the pathophysiology of these conditions.

COMPUTERIZED TRANSAXIAL tomography (CTT), a unique noninvasive radiologic method of imaging the density of tissue, was developed by Godfrey Hounsfield, a senior research scientist at EMI Research Laboratories at Middlesex, England. This procedure yields a detailed plot of the attenuation coefficients within a cross section of an anatomic region. The attenuation coefficients of the head may be displayed as a quantitative axial tomogram by a practical, commercially available machine, the EMI-scanner, which basically consists of a high-voltage source, scanning frame, and computer with its related software and peripheral equipment such as a line printer and cathode ray tube (CRT) viewing unit.[1-6]

Features of the EMI Scanner

The components of the scanning frame are an x-ray tube, two scintillation detectors, and a water box. Both the x-ray tube and the two sodium iodide detectors are coupled in parallel so that their alignment remains constant within the scanner. In addition, the x-ray beam and entrance aperture to each scintillation detector is sharply collimated to 3 by 26 mm and 3 by 13 mm, respectively. The patient's head, surrounded by a latex cap, projects into a perspex water box that intervenes between the tube and the detectors.

A linear traverse of the x-ray tube and of the scintillation detectors across the patient's head, as well as a rotation of the entire scanning frame about the head, is essential for the acquisition of appropriate data. During the linear traverse, 160 counts of photon transmittance are obtained. The scanning frame then rotates one degree, and another linear scan by the tube and detectors yields an additional 160 counts. The alternating linear and rotary sequences are stepped through 180°; therefore, 180 cross-meshing records of 160 collimated beams are transmitted to an on-line computer.

From these 28,800 records, the attenuation coefficients within the 24 by 24 cm field that is visualized by each detector are computed in four to five minutes. Since two adjacent linear counts are averaged, the field of each detector is seen as 80 x 80 matrix representing 6,400 points that correspond to the change in photon transmittance within a 3 by 3 by 13 mm rectangular volume. These data are displayed in the digital form as a printout of EMI numbers that are proportional to the attenuation coefficient of the material at each point and in an analog form as a CRT reproduction in which the brightness is proportional to the attenuation coefficient.

The CRT viewing unit permits expansion and contraction of the picture latitude (window width control) as well as a choice of density within the selected tonal range (window level control). Af-

*From the Departments of Diagnostic Roentgenology and Neurology (Dr. Campbell), Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
Address reprint requests to Dr. Houser, Mayo Clinic, Rochester.

ter setting the window width control at one or measure, the density in any region may be determined by increasing the window level until the region in question changes from white to black.[3]

At a window level of zero, the air about the head is black or less dense while the calvarium and its contents are white and more dense (Figure 1A). A portion of the ventricular system is black at the window level of five (Figure 1B), and most of the ventricular fluid is less dense than at [illegible] igure 1C). At 15 (Figure 1D), not only the entire ventricular system is black but also its margins are somewhat obscured by that portion of the white matter that is less dense. At 20 (Figure 1E), only the gray matter and calvarium are white. At 25 (Figure 1F), only a small amount of cortex is white although the calvarium remains white. Therefore, structures that are filled with cerebrospinal fluid usually measure less than 10; white matter ranges from between 10 into the upper teens; cortical gray matter varies between the upper teens to 30 in EMI numbers. The bony calvarium, ranging between 200 and 500 in EMI numbers, is dense.

To ensure that most of the intracranial contents are evaluated, we include the posterior fossa.[2,5] This is accomplished by orienting the plane of the x-ray beam and detectors 20° toward the feet in relation to the canthomeatal line (Figure 2). The lower margin of the first scan is set at the level of the external auditory canals. Three scans or six slices are routinely performed. If the clinician suspects a parasagittal or high parietal lesion, a higher (fourth) scan is obtained. Similarly, a lower scan is obtained if a lesion is suspected to be present along the base of the skull.

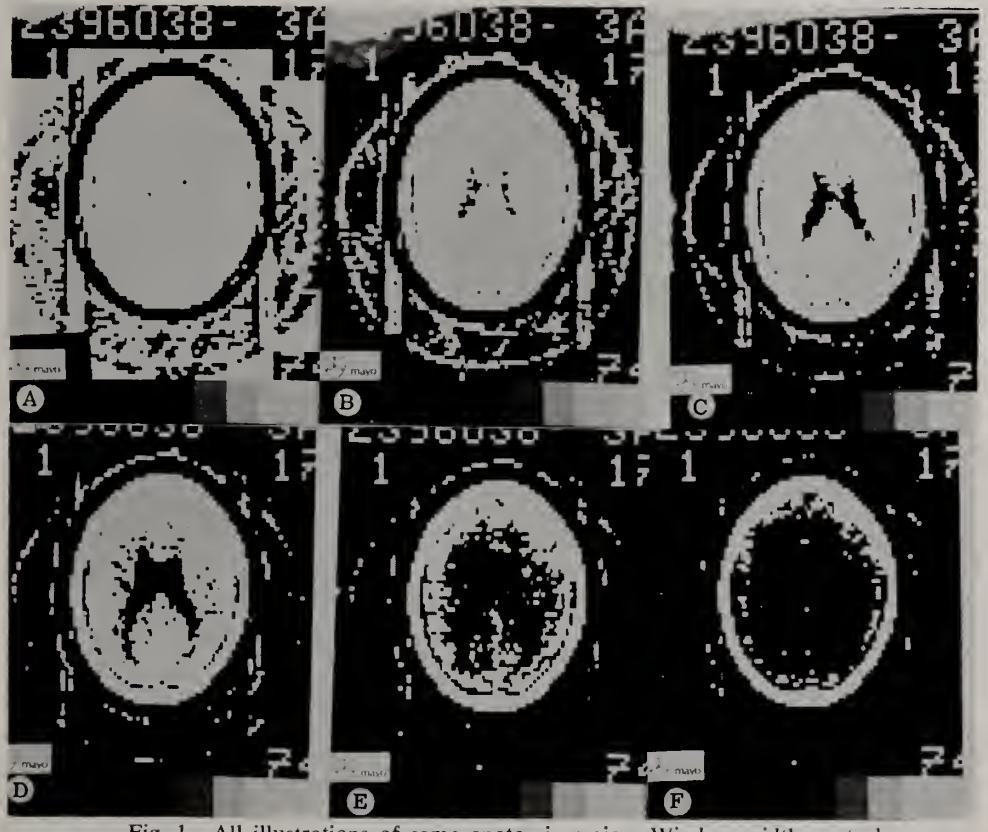


Fig. 1—All illustrations of same anatomic region. Window width control is set at measure and only window level is varied. *(A)* Window level 0. Air about head is black or less dense than 0, while calvarium and its contents are white or more dense than 0. *(B)* Window level 5. Portion of cerebrospinal fluid in lateral ventricles is black or less dense than 5. *(C)* Window level 10. Most of ventricular fluid is less dense than 10. Curvilinear black line (peripheral subarachnoid space) is identifiable between cerebrum and calvarium. *(D)* Window level 15. All of cerebrospinal fluid and some of white matter are black. *(E)* Window level 20. Cerebrospinal fluid and white matter are black. Much of the cerebral cortex and the calvarium are more dense than 20. *(F)* Window level 25. Only small amount of residual cortex and the calvarium are white.

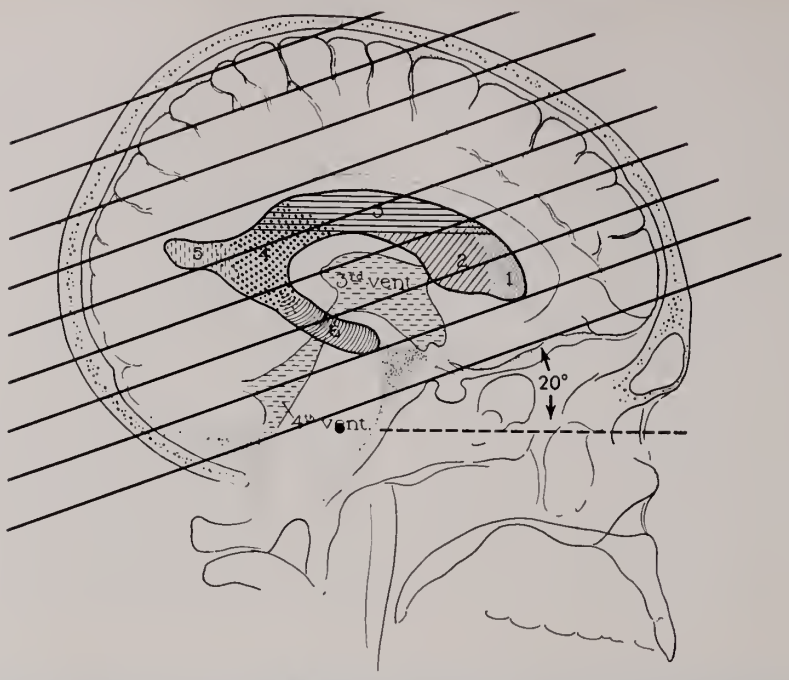


Fig. 2—Plane of x-ray beam and detectors are directed 20° toward feet in relation to canthomeatal line.

(From Baker HL Jr, Campbell JK, Houser OW, et al.: Computer assisted tomography of the head: an early evaluation. Mayo Clin Proc 49:17, 1974).

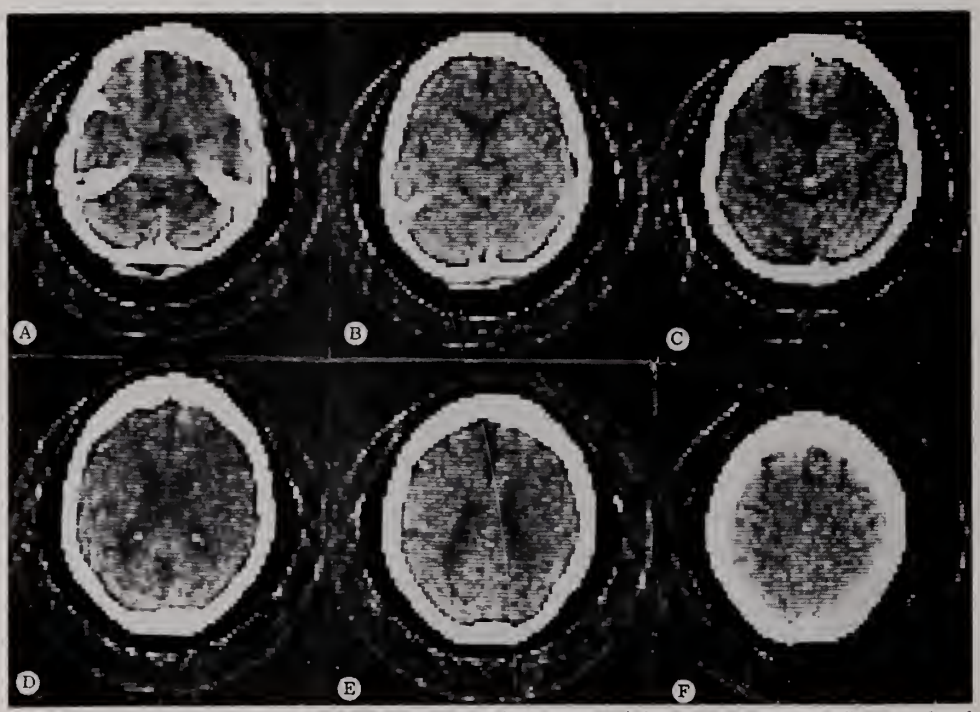


Fig. 3—Usual features revealed by computerized transaxial tomography. *(A)* Lowest level ("slice") demonstrates petrous bones, cerebellar hemisphere, and pons as well as lucent suprasellar cistern and midline fourth ventricle. *(B)* Upper brainstem outlined by cisterns ambiens. Additional lucent structures include frontal horns, third ventricle, and anterior longitudinal fissure. *(C)* In addition to most fluid-filled structures noted in scan *B*, a calcified pineal gland intervenes between ambient cisterns and third ventricle. *(D)* Fluid in lucent anterior and posterior longitudinal fissure as well as lateral ventricles. Note calcification in glomus of choroid plexus bilaterally. *(E)* Only roofs of lateral ventricles are well seen, with corpus callosum between ventricles. *(F)* Parenchyma of brain above lateral ventricles. Note gray matter peripherally is more dense than white matter.

(From Baker HL Jr, Campbell JK, Houser OW, et al.: Computer assisted tomography of the head: an early evaluation. Mayo Clin Proc 49:17, 1974.)

Four scans are necessary in about 15% of our patients.[2]

The Normal Transaxial Tomogram

In general, computer-assisted axial tomography demonstrates the bony calvarium, the parenchyma of the brain, and the cerebrospinal fluid pathways, including the ventricular system, as well as many of the subarachnoid spaces (Figures 3A through F). Because of the high EMI numbers, the bony calvarium appears white on the CRT display or its photographic print. The lucency immediately adjacent to the calvarium may not identify the peripheral subarachnoid space since both computer override and fringing effects are noted at interfaces of structures with markedly different attenuation coefficients.

The subarachnoid spaces about the midbrain and often the upper pons are characteristically depicted (Figure 3B). If the ventricular system is small, only the frontal horns, third ventricle, and fourth ventricle are readily identified. Considerable manipulation of the CRT image may be necessary to portray the body, trigone, and occipital horns of the lateral ventricles in children and young adults. Typically, the ventricular system and sylvian fissures of middle or older age adults are well seen (Figures 3C and D); however, visualization of the temporal horns is unusual unless dilation is pathologic. The visualization of structures, whether cerebrospinal fluid pathways or parenchyma of the brain, depends primarily on their size. Orientation is also important since small structures such as the third ventricle and septum pellucidum are visible because of their vertical position relative to the x-ray beam.

Neither the bony calvarium nor the cerebrospinal fluid pathways are as well visualized by CTT as by routine skull films and pneumography, respectively. The most conspicuous feature of CTT is the parenchyma of the brain. Cortical gray matter is usually more dense than central gray matter,[5] but the head of the caudate nucleus and thalamus are sometimes distinct. Identifica-

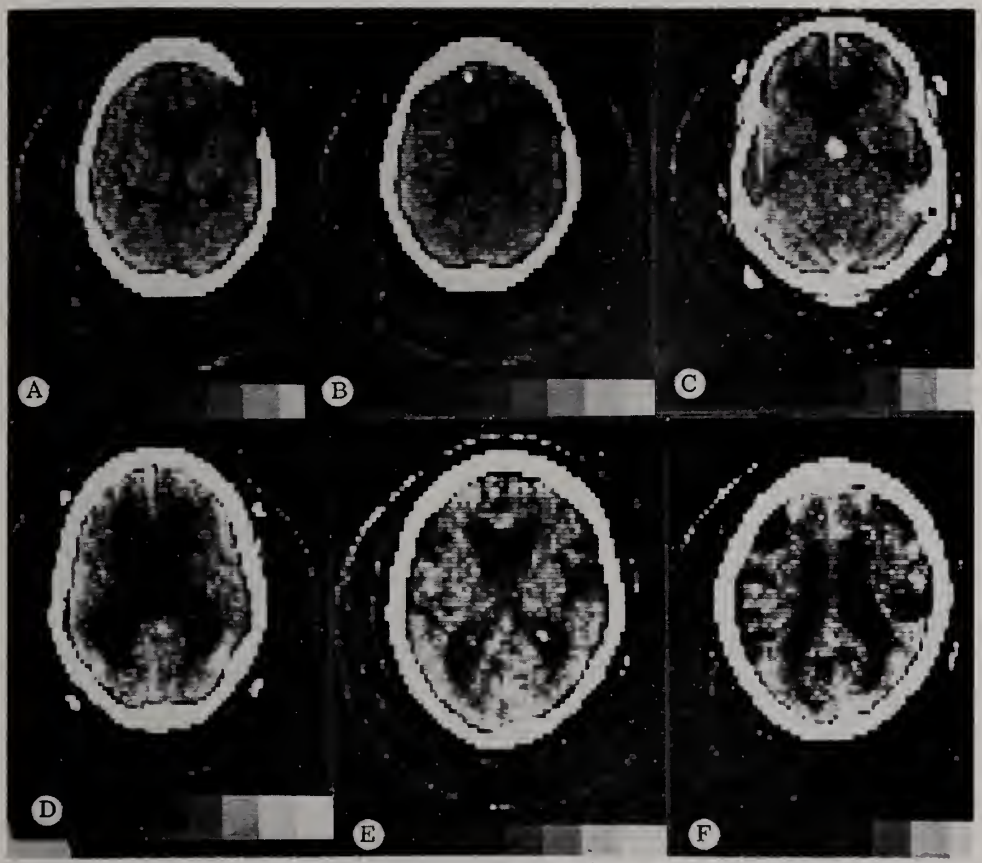


Fig. 4—*(A)* and *(B)* Right frontal skull fracture associated with lucent leptomeningeal cyst and porencephaly of adjacent right frontal horn. *(C)* and *(D)* Dense colloid cyst in anterior third ventricle associated with marked dilation of lateral ventricles. *(E)* and *(F)* Advanced cerebral atrophy associated with enlarged ventricles and markedly widened cerebral sulci.
([C] is from Baker HL Jr, Campbell JK, Houser OW, et al.: Computer assisted tomography of the head: an early evaluation. Mayo Clin Proc 49:17, 1974.)

tion of the pineal gland or choroid plexus usually depends on the presence of calcium in these structures.

The Pathologic Transaxial Tomogram

Several authors[1,2,5,7] have indicated that alterations in the density, gross form, or size of any anatomic structure depicted may be detectable by computerized transaxial tomography. These alterations may reflect the presence of calvarial lesions, deformities or volumetric changes in the ventricles, and alterations in the parenchymal density of the brain.

Sizable defects in the calvarium such as craniectomy sites and spreading fracture (Figures 4A and B) are apparent. However, small defects (including burr holes and even craniotomy deformities) are less obvious and may only scatter the beam. Localized or generalized dilation of the cerebrospinal fluid pathways is easily discriminable. Localized dilation of the ventricles whether congenital or acquired as a result of surgery, trauma (Figure 4B), or atrophy are equally obvious. Similarly, generalized dilation of the appropriate ventricles due to communicating or noncommunicating hydrocephalus is apparent, and distinction between the two is often possible. In patients with obstructive hydrocephalus, not only the level but also the pathologic nature of the obstruction may be inferred if not definitely identified (Figures 4 C and D). A decrease in the parenchymal volume plus an increase in the size of the subarachnoid spaces allows visualization of the gyri and sulci over the convexities of an atrophic cerebrum so that distinction between enlarged ventricles due to communicating hydrocephalus and atrophic or degenerative disease of the brain is often possible (Figures 4 E and F).

Pathologic processes typically alter the parenchymal densities of the central nervous system.[2] The change in density can be mainly an increase, a decrease, or a combination of the two. A localized subtle increase in parenchymal density is ominous and characteristic of either solid primary or metastatic brain tumors (Figures 5 A and B). Intermingled lucencies and densities are somewhat less foreboding since both tumor and infarct may cause this pattern (Figures 5 C and D). A localized decrease in parenchymal density, the most common finding, indicates that fluid is present within the parenchyma. If the lucency is sharply marginated, cystic degeneration may be suspected (Figure 5 E). If the margins are indistinct, the lucency usually represents edema (Figure 5 F). Regardless of the appearance, lucencies per se are nonspecific, and additional features such as the location of the lucency and secondary effects on other structures must be considered.

The secondary effects are best judged by the appearance of the adjacent ventricular system, which may be deformed, obliterated, displaced, or obstructed. If the ventricular system is not affected, a small or medium-sized lucency is usually secondary to a cerebral infarct (Figures 5 C and D); however, extensive edema from a massive acute infarct may deform or even obliterate the adjacent ventricle. If the ventricular system is affected and the abnormality appears proportional to the size of the parenchymal lucency, an intracranial tumor (primary or metastatic) should be suspected. Similarly, a deep parenchymal lucency with associated obstruction, but minimal ventricular deformity, is typical of neoplasm (Figure 5E).

In addition, the striking density of an intracerebral hematoma and colloid cysts suggests that the appearance of CTT may be characteristic, although not necessarily specific for these disorders. In the region of the third ventricle, a dense anterior midline third ventricular tumor, which obstructs the lateral ventricles, would be a colloid cyst (Figures 4C and D). Craniopharyngiomas are typically either calcified or lucent due to their fat content. A glioma adjacent to the third ventricle or suprasellar extensions of intrasellar tumors would show only a slight alteration in density or a decrease in localized density.

The density of clotted blood, allowing precise localization of an intracerebral hematoma regardless of its depth within the brain, is also unique.[1,2,5,7] The appearance of intraventricular clotted blood mimics the ventricular system, whereas the margins of an intracerebral hematoma are often accentuated by the edema in the adjacent brain (Figures 6 A and B).

In contrast to the ventricular system and parenchymal lesions, which are usually well demonstrated by CTT, extracerebral lesions are sometimes difficult to identify unless the difference in density between the cerebral cortex and the lesion are remarkable.[1] It is unfortunate that the common benign lesions such as chronic subdural hematomas and meningiomas fall into this category. A portion of the difficulty is due to com-

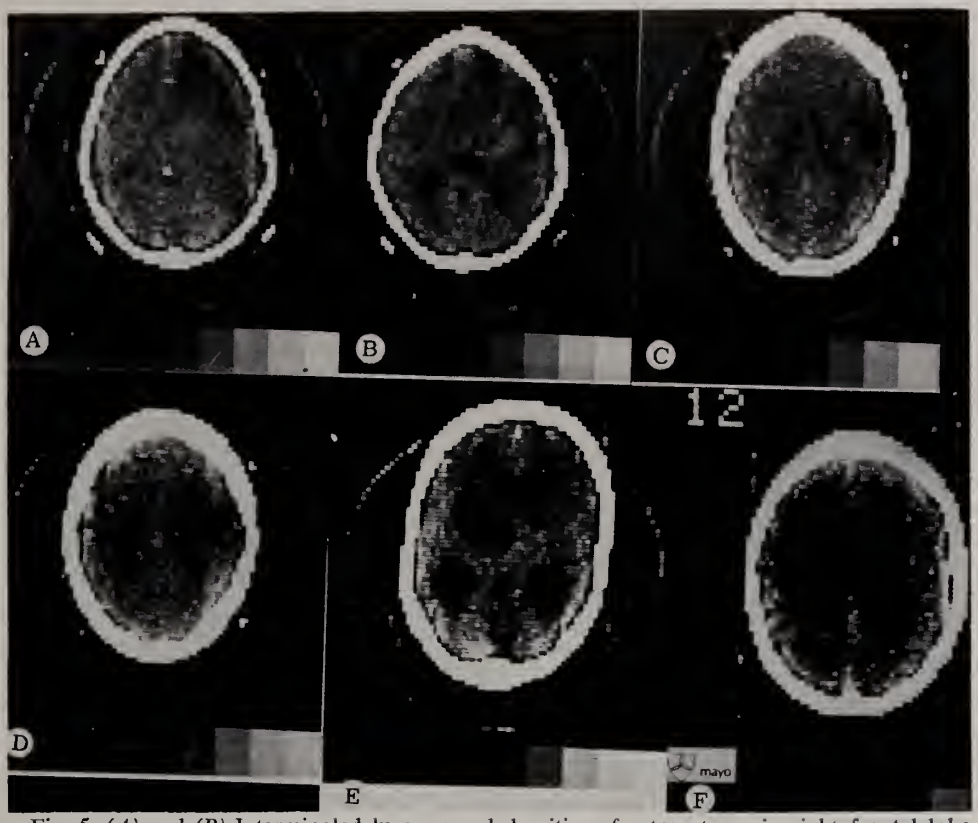


Fig. 5. *(A)* and *(B)* Intermingled lucency and densities of astrocytoma in right frontal lobe. Note shift of frontal horns and calcified pineal gland. *(C)* and *(D)* Ill-defined lucency in right frontoparietal region due to cerebral infarction. *(E)* Cystic astrocytoma involving left basal ganglia and obstructing third ventricle. *(F)* Compression and occlusion of left lateral ventricle due to astrocytoma.

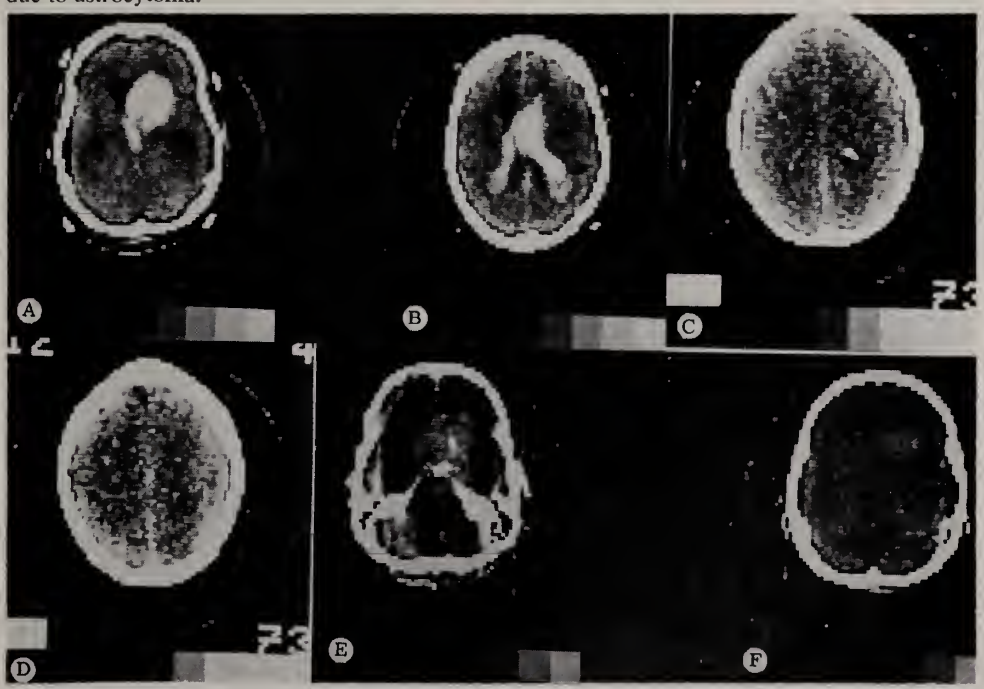


Fig. 6— *(A)* and *(B)* Arteriovenous malformation in head of caudate nucleus. Hemorrhage ruptured into lateral ventricle. *(C)* and *(D)* Subtle increase in density peripherally due to bilateral subdural hematoma. *(E)* and *(F)* Well-circumscribed density of bifrontal and right anterior clinoidal meningioma. Note shift of ventricles and marked edema in frontal lobes (especially the right). (A is from Baker HL Jr, Campbell JK, Houser OW, et al.: Computer assisted tomography of the head: an early evaluation. Mayo Clin Proc 49:17-27, 1974.)

puter override and fringing effects from the adjacent bone, but associated edema in the parenchyma may capture the examiner's eye to such an extent that an extracerebral location of the lesion is not appreciated. As the subdural hematoma undergoes liquefaction, the hemoglobin is resorbed so that the density of residual collection may be similar to that of the cerebral cortex. If the subdural hematoma is unilateral, the presence of a mass is obvious, but its extracerebral location may be difficult to determine. Bilateral subdural collections may be even more distressing since, in the absence of a ventricular shift, neither collection may be identified (Figures 6 C and D).

Meningiomas are readily visualized when calcium is present, the mass is somewhat globular, or the adjacent brain is edematous (Figures 6 E and F). In some instances, the edema tends to obscure the adjacent meningioma unless contrast medium is injected to enhance the density of the tumor.

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"Listen to me. In that bottle, which in other days has held mony a gill o' brandy, there are now sax dizen of as good leeches—black doctors, I should rather call them—as ever swam in water. When I take them to Dr. Clapperton of Loughmaben, or Dr. Laing of Dumfreesh, I'll get ninepence the dizen for them . . ."

"But Nanse," I said, "winna the demand wear out?"

"Will human wretchedness wear out?" she said, sharply. "Winna there be fevers, and brashes, and inflammations, and sudden swellings; beside bruises at fairs, and drinkings, and preachings? Fule girl! wickedness and folly will never wear out, and leeches will aye be wanted!"*

*"Rustic Controversies. The Water Kelpie" (probably by Allan Cunningham), Fraser's Magazine for Town and Country, 1841.

Radiologic Diagnosis of Pulmonary Embolism

JOHN B. MARTA, M.D.*

Pulmonary embolism, often silent and frequently unsuspected, requires awareness of its possible existence in any patient. Because only one patient in five with pulmonary emboli has clinical symptoms, knowledge of which diagnostic procedures will benefit the patient is of great importance.

PULMONARY EMBOLISM is the most common serious clinical problem affecting the pulmonary vascular system.[19,26] It is frequently silent and unsuspected. Emboli are of many types. Thromboemboli are by far the most common; other types include fat, septic, atheroma, parasites, tissue, and foreign matter.[9] Patients most susceptible to pulmonary embolism are those with underlying cardiovascular disease, chronic obstructive pulmonary disease, surgery, hip fractures, and those at bedrest.

The incidence of pulmonary embolization with or without infarction is reported in a variety of ways. In autopsy series, pulmonary emboli have been found in 16% to 64% of the deceased.[12,27] It may be the most common cause of sudden, unexpected death in the hospital. According to McIntyre, Sasahara and Sharma[27] the "postmortem incidence of significant pulmonary embolism (occlusion of two or more segmental pulmonary arteries) was 25% before the routine use of lung scanning and angiography." They also reported that a 2-year prospective study yielded a 2% incidence of clinically detectable pulmonary embolism in a hospital population. It has been estimated that there are as many as 50,000 deaths per year due to pulmonary emboli.[7]

The following statistics on pulmonary embolism have been obtained from two Minnesota hospitals.

Hennepin County General Hospital records† show:

Year	No. of Discharges excluding newborns	No. of Cases of Pulmonary Embolism Diagnosed: Primary Diagnosis	Secondary Diagnosis	Total No. of Cases
1969	12,178	—	—	57
1970	12,991	—	—	77
1971	12,154	—	—	73
1972	3,945 (first 3 months)			25
	9,824 (last 9 months)	32	44	76
1973	12,583	40	69	109
5-year average	12,735			83

At Charles T. Miller Division of United Hospitals in St. Paul:

Year	No. of Discharges including newborns	No. of Cases of Pulmonary Embolism Diagnosed: Primary Diagnosis	Secondary Diagnosis	Total No. of Cases
1969	12,062	22	46	68
1970	12,978	35	56	91
1971	12,860	29	80	109
1972	12,029	62	87	149
1973	11,491	71	64	135
5-year average	12,284	43.8	66.6	110.4

*Department of Radiology, United Hospitals, St. Paul, Minnesota.

†Courtesy of Shih Tsai, M.D.

It is interesting to note that the frequency of diagnosis about doubled in each institution over a five year period with a nearly stable number of patients discharged. This is even more disconcerting if one considers Dalen and Dexter's[3] statement that, based on traditional clinical concepts, our diagnostic accuracy approximates only 50%. If one applies McIntyre, Sasahara and Sharma's[27] finding of a 2% incidence of pulmonary embolism to the above hospital figures one would expect a possible annual incidence (based on a five year average) of 250 cases instead of 83 and 110 respectively.

Signs and symptoms of cardiopulmonary distress in a high risk population should be useful in helping to suspect this disease. Data from the Urokinase Pulmonary Embolism Trial (UPET) study sponsored by the National Heart and Lung Institute, National Institutes of Health, in which 14 institutions pooled information on 160 patients[41] were summarized by Sasahara[34] as follows:

Incidence of Clinical Symptoms and Signs

	All Patients	Massive* Embolism	Submassive Embolism
Dyspnea	81%	79%	83%
Pleural Pain	72	62	84†
Apprehension	59	61	56
Cough	54	50	60
Hemoptysis	34	27	44
Sweats	26	27	24
Syncope	14	22†	4

*Massive is defined as obstruction of 40% or more of the pulmonary vascular tree.
†Can massivity be distinguished? Only two findings so suggest:
Pleural pain more apt with smaller pulmonary emboli
Syncope more apt with massive pulmonary emboli.

Presenting Signs (the more common are non-specific)

	All Patients	Massive Embolism	Submassive Embolism
Rales	53%	50%	57%
Pulm. 2nd sound	53	60*	44
Phlebitis	33	42	21
S_3 S_4	34	47*	17
Sweating	34	41	24
Cyanosis	18	28*	6

*If a patient has cardiorespiratory distress, a loud P_2 indicative of pulmonary hypertension, S_3 or S_4 gallop sounds indicative of some cardiovascular strain and cyanosis plus overt hypoxemia, the patient is more apt to have massive pulmonary embolism than submassive.

The above information is pertinent, even in a radiological article, because the patient's history and physical examination are basic to diagnosis and treatment. The diagnosis must be suspected before ordering the appropriate confirmatory studies.

Many diagnostic modalities have been used to more accurately diagnose or prevent pulmonary embolism. These include, in addition to the history and physical examination, chest radiography, electrocardiography, serum lactic dehydrogenase (LDH), serum glutamic oxaloacetic transaminase (GOT), bilirubin, and arterial pO_2 determinations, limb venography, electrical impedance phlebography (plethysmography), diagnostic ultrasonography,[37] thermography, lung imaging with radiopharmaceutical compounds, pulmonary angiography with or without hemodynamic measurements, ^{125}I fibrinogen tagging of venous thrombi, and radionuclide venography.

Either individually, or as a triad, measurements of LDH, GOT and bilirubin are no longer felt to be of use in diagnostic or therapeutic decisions.[23,27,36] An arterial pO_2 of less than 80 mm. Hg has been felt to be possibly associated or compatible with pulmonary embolism. Sasahara[34] would prefer to change this slightly so that an arterial pO_2 of more than 90 mm Hg would be normal (no pulmonary embolus) and less than 90 mm Hg might be associated with embolism. He emphasizes that this pO_2 measurement must be properly done. Silverstein and Kim[38] recently reported on a normal pulmonary enzyme, guanyl cyclase, which, when elevated, seemed to indicate pulmonary thromboembolism. This, however, is a very preliminary report.

Electrocardiography is a sensitive if not specific diagnostic method for pulmonary embolism. Many abnormalities have been noted in the broad categories of rhythm disturbances, QRS abnormalities, S-T segment and T wave changes.[25,33,41]

Impedance phlebography has been a useful tool for Sasahara, et al.[35] who report a 95% positive correlation of this method in patients with pulmonary embolism.[34] Kakkar[22] states that this technique is slightly more sensitive than Doppler ultrasonography.

Routine chest radiography in two views, posteroanterior and lateral, are basic to the evaluation of pulmonary embolism. The radiologist is the first to suggest the possibility of pulmonary emboli in approximately 50% of cases from standard chest films alone. This is one good reason for a routine admission chest film; it will serve as a baseline for subsequent embolization evaluation. Multiple signs of embolization seen on chest films

have been reported. Westermark's sign[42] of increased lung lucency is well known. Its presence has been noted infrequently and is rare in the experience of others.[7] Hampton's "hump" is seen with infarction.[16] It is a truncated cone involving one or more pleural surfaces with its density due to peripheral alveolar consolidation. Fleischner[11] collated many of the features of pulmonary embolism. Fisher[10] collected and compared reported series which described the frequency of the radiologic signs of pulmonary embolism. Her classification is as follows:

- **(A) Changes due to vascular obstruction**
  - **(1) Hyperlucent lung**
  - **(2) Small hilum**
  - **(3) Dilated pulmonary artery**
  - **(4) Cutoff peripheral vessel**
  - **(5) "Pruned" hilum**
  - **(6) Visible bronchial collaterals**
- **(B) Secondary changes in the cardiovascular system (which also reflect obstruction)**
  - **(1) Cardiac enlargement**
  - **(2) Bulging pulmonary outflow tract**
  - **(3) Distended superior vena cava and azygos vein**
  - **(4) Pleonemia**
  - **(5) Cor pulmonale**
- **(C) Secondary changes in the lungs and the pleurae**
  - **(1) High diaphragm**
  - **(2) Atelectasis**
  - **(3) Pleural fluid**
- **(D) Infarction**

The UPET study disclosed the following incidence of radiographic abnormality.[34]

Finding	Percentage of Patients
Consolidation	41*
High diaphragm	41*
Pleural effusion	28
Plump pulmonary artery	23
Atelectasis	20
Left ventricular enlargement	16
Focal oligemia	15
Right ventricular enlargement	5

Talbot, et al.[39] found that the most useful radiographic sign was elevation of the diaphragm, often with slight atelectasis and a small unilateral effusion. They reiterated a well known fact that the plain chest radiograph is of little value in diagnosing pulmonary embolism without infarction.

Contrast venography, particularly of the legs, is a hallmark technique to identify the most frequent site of origin of thrombi which may embolize to the lungs. Its accuracy is about 90 to 95%. Most other techniques such as Doppler ultrasound, impedance phlebography, ^{125}I fibrinogen tagging of leg thrombi and radionuclide venography are compared to contrast venography for assessment of their accuracy. Between 60 and 80% of pulmonary thromboemboli originate from leg veins. A patient with a normal chest radiograph, a characteristically postive lung scan and a positive venogram has a high probability of pulmonary embolism.

Lung imaging with a rectilinear scanner or gamma camera is the major screening test for pulmonary embolism. It is simple[15] and safe. A negative lung image nearly always rules out pulmonary thromboembolism. Partially occluding emboli may be missed, but are uncommon. The problem with this technique is its lack of specificity. Many diseases can cause perfusion defects. Common causes of defects are chronic obstructive pulmonary disease, neoplasm, pneumonia, congestive heart failure, pleural effusion, atelectasis and air trapping. A good study must include four views of the lungs (anterior, posterior and both laterals) with standard posteroanterior and lateral chest radiographs obtained at the same time. Findings consistent with pulmonary embolism are bilateral, asymmetrical, focal perfusion defects, segmental or lobar in type, many abutting upon the pleural surface. Lobar defects are more likely to be substantiated by pulmonary angiography. This emphasizes the complementary relationship of these two procedures. Angiography is more likely to demonstrate emboli in larger vessels but cannot record embolization to very small peripheral vessels (capillary bed). The latter condition is more readily suggested by radionuclide imaging. These defects change over a period of days to weeks and may be observed with sequential imaging. The change in the appearance of perfusion defects is usually due to clearing of thromboemboli. It may also be due to fragmentation and shifting of emboli in the pulmonary arterial tree. Another reason for a changing perfusion defect pattern is recurrent pulmonary embolism.[43] Moser, et al.[31] reported an uncommon entity of spurious scintiphotographic recurrence of pulmonary emboli. These spurious recurrences reflect changes in the regional distribution of pulmonary vascular resistance secondary to different rates of embolic resolution or distal migration of emboli. The diagnosis of embolic recurrence based on scintiphotos alone should be made with caution especially in patients with multiple emboli and pulmonary hypertension. The requirements for this imaging circumstance are: multiple pulmonary

emboli, emboli of sufficient magnitude to induce persistent pulmonary hypertension and emboli must resolve at variable rates. Clearing of perfusion defects is related to age of the patient, with decreasing clearance associated with increasing age. Patients 60 years of age and older often do not clear their embolic defects[13] but lack of clearing can occur at any age. Some perfusion defects may never clear. Sequential examinations are reliable particularly in the absence of reversible pathological conditions such as asthma, pneumonia and congestive heart failure. These conditions are readily assessed by plain chest radiography. Lung perfusion images must be examined with chest radiographs obtained at the same time. This will eliminate many errors of interpretation. The "fissure sign" originally was felt to reflect microemboli causing peripheral hypoperfusion resulting in bands of diminished to absent radioactivity along the interlobar fissures.[14] Subsequently, multiple processes have been found to produce the fissure sign. Pleural effusion is the most common cause, it is responsible for this appearance in more than 50% of instances.[2,19] Other reported causes are pulmonary edema, emphysema, thickening of interlobar fissures, chronic lung disease, and occlusion of pulmonary lymphatics.[2,19,32] Various imaging techniques are useful. Ventilation studies using the radioactive form of the noble gas xenon can increase the specificity of perfusion imaging in acute pulmonary embolism. Typically, the perfusion defects will not match the ventilation defects since pulmonary ventilation is not impaired in acute pulmonary embolism.[4,5,8,24,29] Unfortunately, small defects may not be evaluated by xenon ventilation.[28] This is an important differential examination and will be used with increasing frequency. If massive pulmonary embolism is suspected (see under clinical signs and symptoms) a scintiangiogram obtained during the injection of the radiopharmaceutical may be diagnostic. When a main right pulmonary artery embolus is likely, injection should be via a leg vein so radioactivity will not pass through the superior vena cava and obscure the main right pulmonary artery as seen in the anterior view. This technique can readily outline major vessel occlusion. Although radioiodinated macroaggregated albumin has been the most common radiopharmaceutical for study of lung perfusion technetium 99m tagged to human albumin in microspheres or macroaggregated albumin is the current agent of choice. Radioactive particle perfusion is very safe, but caution should be taken in patients with a right-to-left cardiac shunt and advanced pulmonary vascular hypertension.

Technetated microspheres are also the radiopharmaceutical of choice in performing radionuclide venography[17] a technique first reported by Henkin, Yao, Quinn and Bergan in 1973.[18] This procedure will detect 90-95% of deep venous thromboses in the lower extremities. It is most reliable from the popliteal region proximally to the inferior vena cava. Its accuracy in detecting thrombi in the calf veins is limited because of hot spots and variability in calf venous drainage. Occlusions, collateral channels and areas of increased radiopharmaceutical concentration can be seen in positive studies. The first two are due to obstruction, the latter to tagging of thrombi. Henkin, et al.[18] feel that pelvic collateral veins are better seen with radionuclide venography than with contrast venography. This procedure necessitates the use of a gamma camera. A high sensitivity collimator is used since the image quality is related to statistics and not resolution. A cart with a moving top and wheel locks is most useful in speeding up the examination. Thirty minutes is the average amount of time needed to complete the study. Butterfly needles (19-25 gauge) are inserted in a dorsal pedal vein of each foot. The knees are identified by radioactive markers on the skin. Injections are made with tourniquets at the ankles to force the radioactive bolus into the deep venous system. Images are made of the areas of interest, e.g. abdomen and pelvis for inferior vena cava and iliac veins, thighs for femoral veins, knees for popliteal veins and calf if desired. A separate injection is used for each area of interest. The two legs must be imaged separately. This study has the advantage that lung perfusion imaging can be performed after the completion of the venography. It also is complementary to the ^{125}I fibrinogen thrombus study since the latter procedure is not applicable to the thigh and pelvic regions. Radionuclide venography may demonstrate formed inactive thrombi that the fibrinogen test cannot. The proponents of this technique[17] feel that it is safe, accurate, and relatively painless. It is especially useful with patients with pulmonary embolism. Unlike contrast venography, it does not have the possibility of idiosyncratic reaction to contrast medium. Patients who have experienced both procedures tend to favor radionuclide

venography.

Pulmonary angiography remains the only specific diagnostic procedure for pulmonary embolism. The direct signs include defects visible within an artery and occlusion of an artery. Indirect signs, which are unreliable, include localized slowing of flow, a decreased number of vessels opacified or atelectasis.[1] Some physicians will not accept non-filling as a diagnostic sign.[28] Contrast medium injection should be made in the main pulmonary artery. Right atrial and/or ventricular injections are less desirable. Peripheral venous injection with "forward" angiography is usually unacceptable. Selective main, lobar and segmental artery injections with oblique and lateral views may be needed, plus the use of magnification,[1] cineangiography,[30] and stereoangiography.[27] Subtraction films may be useful. Special views and techniques are employed due to vessel overlap, contrast medium dilution, blood flow diversion from sites of emboli and variable density of chest structures superimposed upon pulmonary arteries. These angiographic problems frequently can hamper visualization of the signs of embolization. Emboli in tiny peripheral arteries may not be able to be demonstrated even with the special techniques.

Ancillary tests are frequently obtained during pulmonary angiography. Some of these are determinations of pulmonary artery wedge pressures, pulmonary artery, right ventricle and right atrium pressures. Arterial blood gas studies may also be measured; these might include partial oxygen pressure, partial carbon dioxide pressure, pH, oxygen saturation and carbon dioxide content.[40] Pulmonary angiography should at least be considered, if not performed, in all patients in whom irreversible surgical procedures are to be done. Surgery in this category includes vena cava ligation, clipping or plication, Mobin-Uddin umbrella placement and pulmonary artery embolectomy (a rare procedure currently). Fat embolism may not be demonstrable by angiography.

The ^{125}I fibrinogen test[21] is being used with enthusiasm in Europe and by many researchers or AEC board license holders in the USA. The Food and Drug Administration has not licensed this test for general use because of its concern with the possibilities of transmission of hepatitis.[40] Radioiodinated fibrinogen is injected intravenously. Counts are recorded daily at selected sites on the posterior side of the lower leg and anterior surface of the thigh. These counts are most readily compared to precordial counts and expressed as a percentage. This can be done at the patient's bed. The equipment used is simple, consisting of a properly collimated sodium iodide crystal and a ratemeter or scaler. The crux of this test is that a thrombus must be forming, if it is already formed, the fibrinogen will not adhere to its surface. The legs must be elevated 30° to prevent venous pooling which can cause false positive counts. This test is not useful proximal to the midthigh due to radioactivity in the bladder and trunk. This has not been a serious disadvantage since thrombi tend to form in the calf and as they propagate proximally the test will identify the growth of thrombus. Calf thrombi seldom become significant emboli clinically, those in the ilcofemoral veins are of concern. Another problem is time and manpower. A fast examination takes 15 minutes, but 30 minutes are often needed in ill or uncooperative patients. With an active surgical service, this test could be time and manpower consuming. Dworkin calculated an approximate cost of $300 per patient for this examination at William Beaumont Hospital in Royal Oak, Michigan. Serum hepatitis has not been significant, only one case is known to date.[5] Other limitations are the tagging of hematomas and recent wounds[5] plus false positive results in the presence of acute arthritis, varicose ulcers, cellulitis, local trauma, superficial thrombophlebitis or gross leg edema.[40] This test has been found to be 90-95% accurate in the identification of forming thrombi.[5,21] False positive and false negative results are less than 5%. It is recommended as a screening and/or prospective type of test[5,21] for medical, obstetric and surgical patients. The advantages of this test are its extreme sensitivity and accuracy *when a thrombus is being formed* in addition to the lack of untoward reactions. It is obviously complementary to the radionuclide venogram.

With this plethora of procedures, is there a simple logical approach to the clinical diagnosis of pulmonary embolism? Many schema have been advocated. A brief version adapted from Sasahara[34] is submitted:

Suspect pulmonary embolism
Administer 10,000 units of heparin
Obtain:
  Chest radiographs, compare to previous radiographs.
  Electrocardiogram, correlate
  Arterial pO_2
    If: more than 90 mm Hg, perhaps stop,

less than 90 mm Hg, go to
Lung imaging, 4 views minimum or
Assay for deep venous thrombosis with:
Impedance phlebography or
Doppler ultrasonography or
Contrast venography or
^{125}I fibrinogen test or
Radionuclide venography in conjunction with lung imaging
If these tests are abnormal, do lung imaging.
If data indicate pulmonary thromboembolism, treat with anticoagulants.
If surgery is indicated due to anticoagulant failure, (an uncommon occurrence), obtain a pulmonary angiogram because surgery is an irreversible invasive procedure and emboli should be positively identified.

Acknowledgments

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iagnostic Approach to Renovascular Hypertension

C. RICHARD DUNN, M.D.*

Determination of renal vein renin and angiography are the best available techniques for detecting surgically curable renovascular hypertension.

RENOVASCULAR HYPERTENSION was first suspected as a clinical entity in the mid-nineteenth century following Bright's publication of his personal observations in renal disease.[1] Renin, a pressor substance released systemically by the ischemic kidney, was shown to be capable of producing hypertension in 1898.[2] Goldblatt developed the experimental model of this potentially curable cause of high blood pressure.[3] He placed a ligature around the renal artery, recorded the sustained increase in blood pressure accompanied with increased renin plasma activity, and demonstrated that both would return to normal when the kidney was removed.

Selection of hypertensive patients who may benefit from a surgical procedure remains one of the most difficult and perplexing diagnostic problems. Intravenous urography, isotope renography, arteriography, and selective catheterization of renal veins for comparative renin determination have established the radiologist as the physician responsible for this diagnosis. Although current diagnostic techniques are far from ideal, their judicious use and interpretation will improve the outlook for patients with high blood pressure. Oversimplification, on the other hand, may lead to unnecessary surgery that does not result in cure.

Historical Perspective of Current Techniques

In the 1950's and the early 1960's abdominal angiography became widely used in the United States. Many anatomical variations and abnormalities were reported in association with hypertension. These included renal artery stenosis, renal artery aneurysm, renal artery embolus, arteriovenous fistula, renal cyst, vasculitis with microaneurysm, perinephric hematoma, pyelonephritic kidney, and traumatic interruption of renal vascular supply.[4]

The arteriogram proved very sensitive in identifying such vascular and parenchymal lesions (Figure 1). Thousands of people were operated upon because of such angiographic results. The number of surgical cures was far less than expected. It became painfully apparent that the anatomic appearance of the lesion gave little information concerning its hemodynamic significance.[5-8]

Intravenous urography and isotope renogram were, likewise, found to be disappointing as screening tests. Figure 2 illustrates our experience with these two tests in a recent group of patients Eighteen percent of the rapid sequence intravenous urograms were false negative while 23% of the renograms were false negative. This correlates well with the figures reported in the literature.[9,10] It necessarily follows that all patients

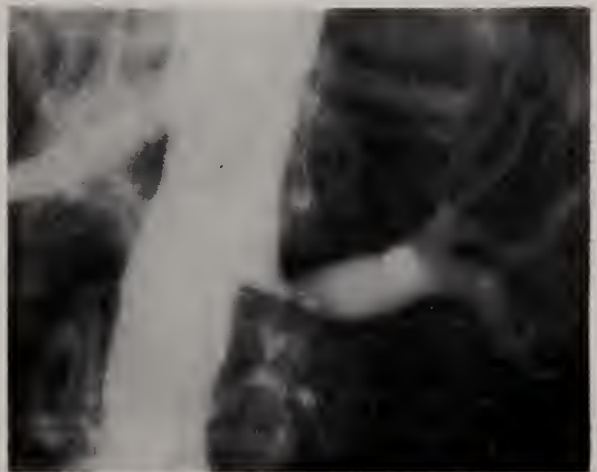


Fig. 1—Severe renal artery stenosis with post-stenotic dilatation is *not* sufficient evidence for surgically correctable renal lesion.

*Department of Radiology, University of Minnesota Medical School, Minneapolis.

that are candidates for surgical correlation of hypertension must have a renal arteriogram.

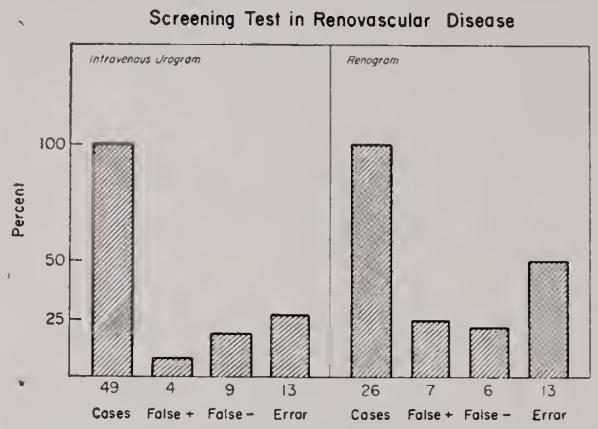


Fig. 2—The intravenous urogram and renogram have high incidence of false negative and positive results.

Since the arteriogram itself could not establish the significance of an anatomic abnormality, physiologic and hemodynamic tests had to be developed to prove decreased blood flow through the involved kidney. Differential pressures across the stenotic lesions, evaluated both by the radiologist during catheterization and the surgeon at the operating table, have often proved inaccurate due to technical difficulties.[4] Split function tests evaluating each kidney separately were introduced by Howard et al.[11] They were associated with high morbidity and were predictive only at the 70-75% level.[12] The urea washout test was based on the same principles as the Howard test but did not require selective catheterization of the ureters.[13] This test did decrease the morbidity but did not improve the accuracy in predicting a surgical cure.

The pendulum of enthusiasm for surgery thus swung toward the negative side, particularly in view of the considerable progress being made with newer drugs that effectively control hypertension. The development of practical laboratory tests for the evaluation of renal vein renin activity has rekindled interest in the diagnosis of hypertensive patients who may benefit from surgery. The most important advance in methodology has been the development of a radioimmunoassay for renin. This test requires only 5 cc. blood samples and permits multiple samples at ten minutes intervals, resulting in a time-concentration curve of renin excretion.

The Best Current Technique

The selective evaluation of renal vein renin activity under conditions of proper stimulation and their correlation with the arteriogram is the current standard for establishing the hemodynamic significance of a kidney lesion. When the two examinations correlate, the surgical cure rate increases dramatically as compared to the cure rate based on diagnosis by angiogram alone.[14-16] Renal vein renin determinations are considered positive when the renin values from one kidney are at least 1.5 x greater than that from the other kidney. No absolute values are placed on renal vein renin activity.

As Figures 3A and 3B illustrate, when the renin values and the arteriogram are both abnormal the clinical decision is made easier. In spite of a normal intravenous urogram, this middle aged female had right renal artery stenosis with post-stenotic dilatation and collateral flow. The renin values suggest a hemodynamic lesion in the right kidney. The diagnosis of renovascular disease which is likely to respond to surgery is made in this fashion. A vein bypass of the stenotic lesion was performed in this patient, and her blood pressure returned to normal.



Fig. 3A—Right renal artery stenosis with post-stenotic dilatation and collateral flow.

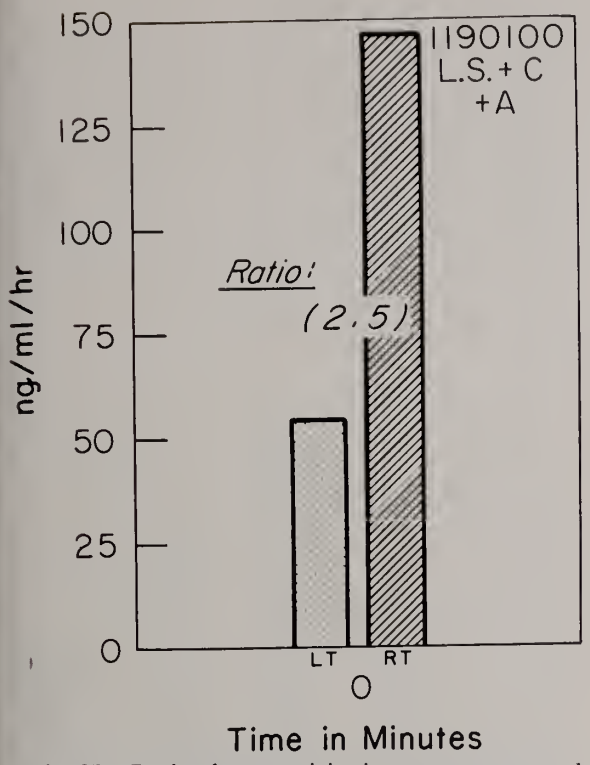


Fig. 3B—Renin plasma activity in nanograms per ml. per hour is 2.5 times as great from the right kidney as left.

When the renins are negative and the angiogram positive, it may mean that the lesion identified on the angiogram lacks hemodynamic significance in the genesis of high blood pressure. When the renins are positive and the angiogram negative, it points to a false negative angiogram.

No negative renin value should be accepted as valid unless the patient has received adequate stimulation for renin release. What constitutes an adequate stress has resulted in some discussion. Reports have appeared that low salt diet preparation coupled with diuretics constitute an adequate stress.[17] Our experience indicates that, regardless of preparatory diet, the patient must receive some stimulus to increase renin release during the collection of renal vein blood. Currently, we collect baseline blood from each renal vein and then inject 20 mg. of Apresoline intravenously and repeat the collection at ten, twenty, and thirty minutes.[16] Upright posture of the patient following the collection of baseline values has also been reported to constitute such a stress.[18] Figure 4 shows the effect of such a stress on renin values in 12 patients which were negative before Apresoline in spite of an abnormal angiogram. Following Apresoline, nine of the twelve, or 75%, gave abnormal renin values that correlated with the angiogram. If the renin production is adequately stressed, as in the three remaining patients, negative renins with a positive angiogram should mean that the anatomical lesion lacks hemodynamic significance, and that surgery will not be helpful.

If the renins are positive and the angiogram negative, a careful re-examination of the patient should be performed utilizing oblique projections and magnification techniques. False negative arteriograms are much more common than we think, because the search for the lesion stops when the arteriogram is read as normal.

Figure 5 depicts such a case. This college student developed sudden hypertension following a

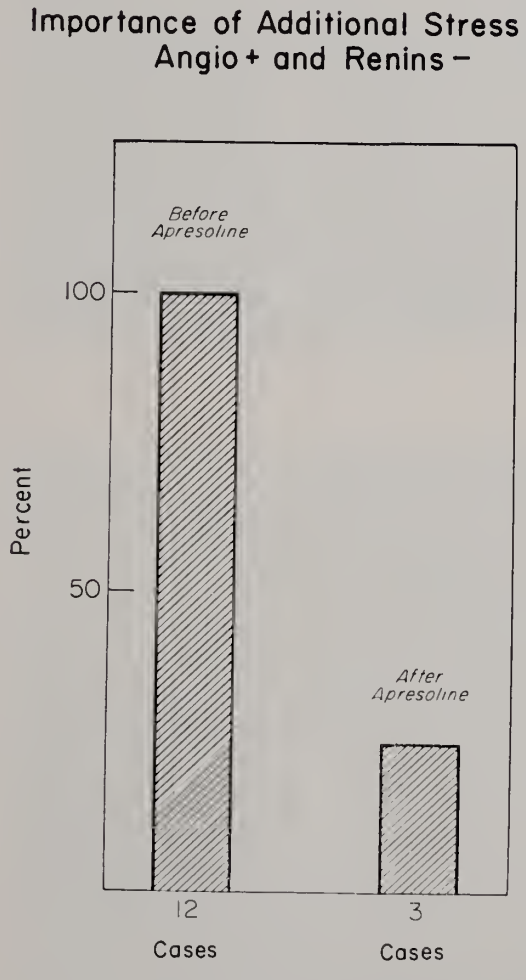


Fig. 4—Twelve patients with positive angiograms had negative baseline renins. Following the stress of Apresoline nine of the twelve converted to positive correlating with the angiogram. The negative renins in the remaining three patients suggest the lesion identified on the angiogram will not respond to surgery.

renal biopsy. The angiogram (Figure 5A) was read as negative. The renin values (Figure 5B) suggested a hemodynamically significant lesion in the right kidney. Re-examination using magnification oblique views demonstrated an aneurysm of an intrarenal artery (Figure 5C) and a peripheral scar (Figure 5D). Segmental stenosis and small infarcts are easily missed at angiography. The search for a surgically correctable lesion should resume when the laboratory returns renin values that are positive.

Summary

It remains the responsibility of the clinician to determine if a hypertensive patient is a potential candidate for surgery. All such candidates, especially children through middle aged adults, must have an arteriogram and renal vein renin determinations regardless of the results of the intravenous urogram or renogram. If the arteriogram and renin values correlate, the clinical decision is made easy. If the renins are positive and the angiogram is negative, the latter should be re-



Fig. 5A—See text.

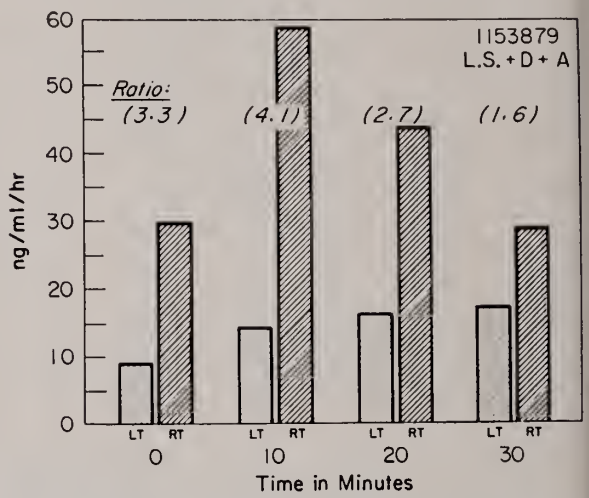


Fig. 5B—Comparative renin values from right and left kidney at zero time or baseline values and ten, twenty, and thirty minutes following injection of Apresoline.



Fig. 5C—See text.



Fig. 5D—See text.

peated in search for lesions that may have been missed. If the angiogram is positive and the renins negative, then the anatomic lesion most likely lacks hemodynamic significance.

Selective renal vein renin determination, although valuable in this disease, is not an ideal examination. It can be a very long, tedious procedure and involves a small but definite risk to the patient. The final determinations are made by a prolonged radioimmunoassay of the serum and the results are not available for several days. Currently research is being conducted to find a safe, fast method for evaluating the significances of arterial abnormalities at the time the angiogram is done. Until such research is successful renin determination remains the best tool we have to evaluate the hemodynamic significance of the anatomic lesion identified by angiography.

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Dr. Douglas Fenderson

Dr. Douglas Fenderson has been named director of the University of Minnesota's office of continuing medical education and associate professor in the hospital and health care administration program.

A Minnesota native, Fenderson earned his bachelor's degree at the University of Minnesota in 1952, his master's in 1956 and his doctor of philosophy in educational psychology in 1966.

Intussusception: Facts, Fallacies and Practicalities

HUGH J. WILLIAMS, M.D.*

More misconceptions are associated with intussusception in infants and children than with any other commonly encountered pediatric disorder. Hopefully, this article will dispel some of these fallacies.

INTUSSUSCEPTION IS THE telescoping of one segment of gut into another. The telescoping segment of bowel is known as the intussusceptum, the recipient segment the intussuscepiens. Transient, asymptomatic telescoping of a portion of small bowel into an adjacent loop is frequently observed in children during small bowel barium studies. It is conceivable that such transient intussusceptions may produce distress and constitute one of the causes for "indeterminate abdominal pain" so frequently encountered in children.

Intussusception may occur at any age, but is most frequently encountered under two years of age, with the peak incidence occurring between the third and eleventh months. Over 90 percent occur in infants and children. There is a two-fold male predominance. It is the commonest cause of intestinal obstruction between the ages of two months and five years. It is second only to appendicitis as the commonest acute abdominal condition in children.

Etiology

In contrast to adults where an underlying cause for the intussusception is usually present, in 90% of infants and children no causative mechanism can be demonstrated. Despite numerous attempts to explain idiopathic intussusception on the basis of abnormal peritoneal folds at the ileocecal junction[2] or hypertrophy of Peyer's patches in the distal ileum secondary to an adenoviral enteritis,[3] the etiology in most cases remains uncertain. In the 10% of cases in which a precipitating factor is demonstrable, Meckel's diverticulum is the most frequently encountered cause. Lymphoid hyperplasia of the distal ileum and various tumors, including small bowel wall hemorrhage may also precipitate intussusception.

Small bowel intussusception is a frequently overlooked cause of small bowel obstruction in the post-operative period, since the presenting symptoms often consist only of abdominal distention and vomiting without associated abdominal mass or rectal bleeding.[4]

Types of Intussusception

There are four types of intussusception encountered in children (Table). In the most commonly occurring type, ileocolic intussusception, the ileocecal valve and terminal ileum, with or without the cecum, telescope into the colon for a variable distance (Figure 1). In ileoileocolic intussusception a primary ileoileal intussusception advances through the ileocecal valve into the ascending colon. Pure enteroenteric intussusception most commonly occurs in the ileum but is also frequently encountered in the jejunum (Figure 2). Colocolic intussusception is unusual in children (Figure 3) and is often associated with a lead point such as a lymphomatous mass.

TABLE
Types of Intussusception

1. Ileocolic	85%
2. Ileoileocolic	10%
3. Enteroenteric intussusception	4%
4. Colocolic	1%

Some of the more commonly encountered facts and fallacies relative to intussusception, with illustrative examples from our experience at the St. Paul Children's Hospital, will now be presented.

I. Fact or Fallacy? The clinical diagnosis of intussusception is easy because the clinical picture is so characteristic.

Fallacy

The clinical diagnosis of intussusception is often

*Department of Radiology, The Children's Hospital, 311 Pleasant Avenue, St. Paul, Minnesota.



Fig. 1—The arrow indicates the site of an ileocolic intussusception in this nine-week-old infant. The cecum and appendix are visible and do not form a portion of the intussusception.



Fig. 2—The barium filled colon and distal few centimeters of distal ileum are normal. The filling defect in the ileum (arrow) represents an ileoileal intussusception led by a Meckel's diverticulum.

difficult and its symptoms overlap those of many other conditions. Pain is present in 95% of affected individuals and vomiting in 75%, but both of these symptoms are also common in gastroenteritis and bowel obstruction. Bloody stools, long considered a hallmark of intussusception, are a late finding and are present only in 50% of children with symptoms of over 24 hours duration. When symptoms have been present for less than six hours, grossly bloodly stools are encountered in 30% of infants under one year but in only 5% of children over one year of age. The classical textbook triad of pain, vomiting and bloody stools occurs in only 10% of children[5] and insistence on the co-existence of all these findings will delay the diagnosis. The following cases illustrate the difficulty encountered in establishing the diagnosis clinically early.

Case Reports

Case 1

A four-year-old boy was admitted after several days of mild abdominal pain. The abdominal roentgenogram was interpreted as negative, but in retrospect the soft tissue mass of the intussusceptum was visible and out-



Fig. 3—The large colocolic intussusception located in the cecum of this three-year-old girl was led by a large lymphosarcoma of the ileocecal valve. She is alive and well eight years later.

lined by gas in the left transverse colon (Figure 4A). No cause was discovered for the child's pain and, because he had always been considered a "nervous child," psychiatric consultation was recommended. Three days later, just before the psychiatric examination was consummated, bloody diarrhea developed. A barium enema was immediately performed and an irreducible intussusception was encountered in the transverse colon (Figure 4B). It was subsequently surgically reduced and the patient did well post-operatively.



Fig. 4A (Left)—The soft tissue mass of intussusceptum outlined by air in the left portion of the transverse colon (arrow) of this four-year-old boy with abdominal pain was not appreciated and his pain was ascribed to psychosomatic causes.

B (Right)—O huge ileocolic intussusception was demonstrated by barium enema three days later following the onset of bloody diarrhea. It was incompletely reduced hydrostatically and was corrected surgically.

Case 2

An 11-month-old infant was admitted with the clinical diagnosis of gastro-enteritis. Several members of the family were afflicted with similar symptoms. Because the abdominal roentgenogram demonstrated several mildly gas-fluid distended small bowel loops and failed to reveal a cecal shadow, the possibility of intussusception was suggested. An immediate barium enema demonstrated an intussusceptum in the transverse colon, which was reducible to the cecum but no further (Figure 5). While the diagnosis of intussusception is often relatively straightforward, there are many cases such as these, where the clinical and radiographic findings are anything but classical.

Case 3

A six-month-old infant was admitted with vomiting and grossly bloody stools (currant jelly). Because of the clinical diagnosis of intussusception, a barium enema was performed and surprisingly demonstrated an unsuspected strangulated right inguinal hernia as the cause of the infant's symptoms (Figure 6).

II. Fact or Fallacy? A normal abdominal roentgenogram rules out intussusception.

Fallacy

The abdominal radiograph is normal in one third of cases of intussusception. In another third of cases the soft tissue mass of the intussusceptum is demonstrable roentgenologically (Figure 7). In the remaining third of patients there is non-specific gas and fluid distention of one or more loops of small bowel, encountered



Fig. 5—The clinical and abdominal radiographic findings favored a diagnosis of gastroenteritis in this eleven month old infant. An irreducible ileocolic intussusception, however, was encountered. It is visible in the cecum.



Fig. 6—This three-month-old infant presented with vomiting, abdominal pain and bright red rectal bleeding the classical triad of intussusception. Barium enema however, demonstrated a clinically unsuspected strangulated right inguinal hernia extending into the scrotum (arrow).

usually in the right upper quadrant early, and with involvement of additional loops later. Failure to visualize the cecal shadow in the right lower quadrant is also a helpful finding in some cases. It must be emphasized that the abdominal roentgenogram will be normal or non-specific in two thirds of infants and children with intussusception.



Fig. 7—The soft tissue mass of an ileoileocolic intussusception (arrows) is visible in the right portion of the abdomen of this eleven-month-old infant. There is moderate small bowel gaseous distention.

Case 4

An 11-month-old infant was examined because of a hemorrhagic, soft tissue mass which protruded from the rectum and was thought to represent rectal prolapse. Because of recurrent protrusion of the mass despite several replacements, the infant was admitted to hospital. The abdominal roentgenogram was normal (Figure 8). A barium enema was then performed and demonstrated a large intussusceptum in the rectosigmoid colon which could be only partially hydrostatically reduced (Figure 8-B). We have encountered several cases in which rectal protrusion of the intussusceptum simulated rectal prolapse but in whom complete hydrostatic reduction occurred despite the extent of the intussusception. In order for such extensive intussusception to occur, the involved bowel must possess a long mesentery.

Case 5

A small bowel obstructive pattern was present in this seven-month-old infant with vomiting and abdominal



Fig. 8—The abdominal roentgenogram of this eighteen-month-old infant with "rectal prolapse" is deceptively negative. (Insert)—The barium column is halted at the rectosigmoid junction by a large intussusceptum. The intussusception could only be partially reduced hydrostatically.



Fig. 9—A high grade small bowel obstructive pattern is present in this seven month old infant with abdominal pain but no rectal bleeding. A large ileocolic intussusception was encountered in the transverse colon and reduced to the cecum but no further. Even partial hydrostatic reduction, as in this case, is valuable since it facilitates the surgical operation.

pain but no bloody stools (Figure 9). The clinical diagnosis was small bowel obstruction of undetermined origin. A barium enema demonstrated an intussusceptum in the transverse colon which was reducible to the cecum but no further. At surgery a persistent ileocolic intussusception was reduced. In general, the longer the duration of the intussusception, the more likely it is that a secondary small bowel obstruction will be present. Since the obstructive bowel pattern in intussusception is often indistinguishable from that of other causes of small bowel obstruction, the early diagnosis of intussusception is frequently overlooked.

The classical radiographic finding of intussusception during a barium enema examination is the coil spring, a phenomenon due to barium located between the walls of the intussusceptum and the intussuscepiens (Figure 10). The amount of barium entrapped between the contiguous bowel walls and, hence the degree of coil spring formation, is dependent on the tightness of the intussusception.



Fig. 10—The typical coil spring appearance of an intussusception resulting from barium trapped between the intussusceptum and intussuscepiens (arrow) is clearly visible in the transverse colon of this three-month-old infant. Moderate small bowel gaseous distention is present indicating early obstruction.

III. Fact or Fallacy? It is safe to attempt hydrostatic reduction of an intussusception even when symptoms have been present for over 24 hours.

Fact

The reducibility or irreducibility of an intussusception does not correlate well with the duration of symptoms. A tightly impacted intussusceptum of only a few hours duration may be less reducible than a loose intussusception or an intermittent one of several days duration. Therefore, hydrostatic reduction of any intussusception, regardless of duration, should be attempted if there is no clinical contraindication such as peritoneal irritation.

Case 6

A five-year-old boy was admitted with intermittent abdominal pain of over 36 hours duration. Despite the relatively long duration of symptoms, the abdomen was soft. A barium enema was performed and the ileocolic intussusception which was encountered was readily reduced. He developed recurrent pain 24 hours later and an abdominal roentgenogram revealed a recurrent intussusception in the transverse colon outlined by residual barium (Figure 11). A repeat barium enema was performed and the recurrent intussusception was reduced to the cecum but no further. The child was taken to surgery only to find that the intussusception had spontaneously reduced in the interval. Spontaneous reduction after unsuccessful hydrostatic reduction is not uncommon and is probably related to relaxation of the gut produced by anesthesia.

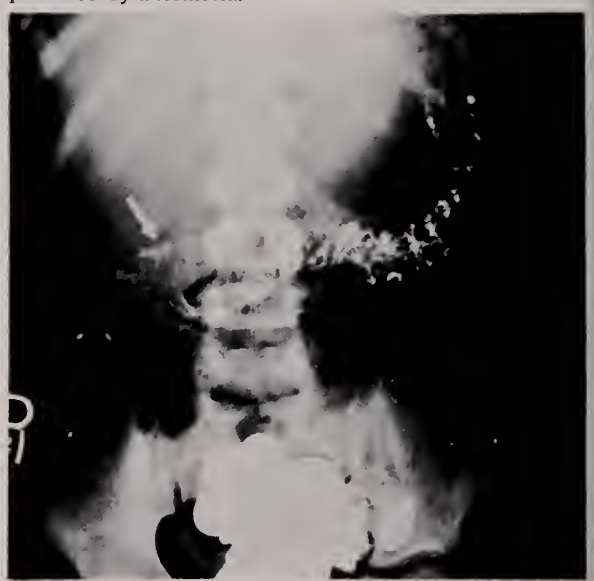


Fig. 11—A recurrence of an intussusception hydrostatically reduced some 24 hours previously is outlined in the transverse colon (arrow) of this infant by residual barium in the bowel from the previous examination.

IV. Fact or Fallacy? Hydrostatic reduction is contraindicated in children over two years of age because a lead point is usually present in such patients.

Fallacy

In comparison to adults, where most intussusceptions are led by a tumor or other mass, lead points are still quite uncommon in children over two years of age. Only 25% of children beyond this age will demonstrate a lead point. In the remaining 75% there is no discernible cause for

the intussusception. When such a lead point is present, hydrostatic reduction is seldom possible, rendering it unlikely that an intussusception led by an organic lesion will be reduced and the lesion thereby overlooked. Nevertheless, because of the relatively frequent association of lymphosarcoma and intussusception in older children, surgery should be considered whenever intussusception is encountered after six years of age (Figure 3).

Case 7

An intussusception was encountered in the transverse colon of a three-year-old boy and completely reduced with extensive retrograde filling of the terminal ileum. Abdominal pain recurred 24 hours later and a repeat abdominal roentgenogram demonstrated a recurrent intussusception at the hepatic flexure outlined by residual barium. A second barium enema was performed and successful hydrostatic reduction of the intussusception was again obtained. Symptoms recurred 12 hours later and surgery was performed with successful reduction of an ileocolic intussusception. Despite the age of the child and three episodes of intussusception no lead point was present at the time of surgery. Four days postoperatively the child again developed abdominal pain. Barium enema once more demonstrated recurrent intussusception and this was again successfully reduced hydrostatically. The recurrence rate of intussusception is approximately 5% following either hydrostatic or surgical reduction. Statistically the chances for three recurrences, as in this child, are only 1:8000.

V. Fact or Fallacy? It is useless to attempt hydrostatic reduction if the abdominal roentgenogram demonstrates a small bowel obstructive pattern.

Fallacy

While the frequency of successful hydrostatic reduction diminishes with the presence of an increasing small bowel obstructive pattern, successful reduction is still obtainable in 50% of children with radiographic findings of small bowel obstruction. Although the presence of a lead point such as a Meckel's diverticulum increases the likelihood of a small bowel obstruction, such lead points are present in only 5% of infants and children. In such cases successful reduction of the intussusception is seldom achieved. For these reasons hydrostatic reduction may be attempted in the presence of a small bowel obstructive pattern, providing there are no clinical contraindications such as peritoneal irritation.

Case 8

This 16-month-old infant was admitted with intermittent crampy abdominal pain of five-days duration. Physical examination and laboratory tests were normal. The abdominal roentgenogram demonstrated a fairly severe small bowel obstructive pattern (Figure 12A). Since there were no clinical contraindications, a barium enema was performed. Successful reduction of the encountered intussusception was readily achieved, despite the long duration of symptoms and the presence of an obstructive pattern. A post-evacuation roentgenogram (Figure 12B) demonstrated a recurrence of the intussusception into the ascending colon. A repeat barium enema was performed and successful reduction of the intussusception was again achieved. There was no recurrence following this second reduction. Immediate recurrence of a reduced intussusception is not uncommonly encountered following successful hydrostatic reduction and for this reason a post-evacuation film should always be obtained. We have also encountered the reverse situation, namely where an intussusception was irreducible and the examination discontinued, only to find that spontaneous reduction was evident in the post-evacuation film.



Fig. 12A-(Left)—A severe small bowel obstructive pattern is present in this sixteen month old infant with intermittent crampy abdominal pain for five days duration. Since there were no clinical contraindications, a barium enema was performed and successful reduction of an ileocolic intussusception was achieved. B-(Right)—A post-evacuation film demonstrated a recurrence of the intussusception into the ascending colon (arrow). A second barium enema was performed and reduction was again obtained. There was no subsequent recurrence.

VI. Fact or Fallacy? The possibility of reducing non-viable gut constitutes a significant hazard during hydrostatic reduction of an intussusception.

Fallacy

There is ample experimental and clinical evidence to prove that non-viable bowel will not be reduced by properly applied hydrostatic pressure.[6] I can recall no instance in my experience where surgery was subsequently required to remove a segment of non-viable gut which had been hydrostatically reduced by barium enema. On the other hand resection is sometimes performed on bowel mistakenly thought to be non-viable or on bowel inadvertently traumatized by the manual reduction itself.[6]

Case 9

A seven-year-old boy with Henoch-Schonlein purpura was admitted with abdominal pain and bloody stools. A completely irreducible ileocolic intussusception was encountered in the mid-transverse colon during a barium enema examination (Figure 13). Immediate surgery dem-

onstrated that the intussusception was led by a large hematoma in the wall of the terminal ileum. The bowel wall was markedly edematous and in some areas early necrosis was present. Manual reduction was impossible and a right hemicolectomy and ileotransverse colostomy were performed. The child did well subsequently. This case demonstrated not only that non-viable bowel is hydrostatically irreducible but also that reduction of an intussusception led by a significant lesion is unlikely.

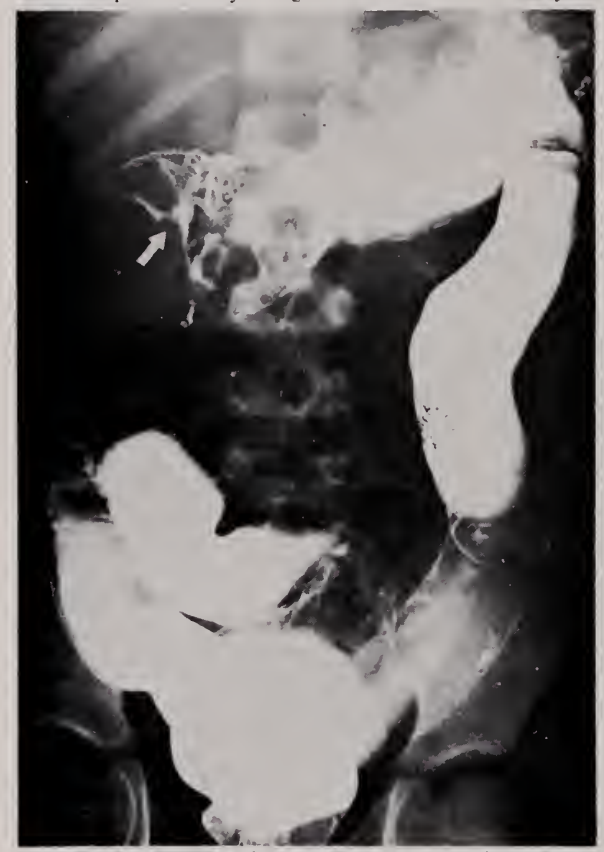


Fig. 13—The large, irreducible intussusception demonstrable in the mid-transverse of this seven year old boy (arrow) was led by an submucosal hemorrhage in the terminal ileum secondary to Henoch-Schoenlein purpura. Surgical reduction was impossible and a right hemicolectomy and ileo-transverse colostomy were performed.

Treatment

Controversy has existed for many years regarding whether intussusception should be treated surgically or by hydrostatic reduction. In the past decade, based on the extensive experience of Nordentoft[7] and Ravitch,[8] the pendulum has swung towards attempted hydrostatic reduction of intussusception in most cases. The two valid contraindications to hydrostatic reduction are evidence of peritoneal irritation and a critical state of illness in the patient. A diagnostic barium enema and attempted hydrostatic reduction is performed at our institution in the vast majority of children whenever the clinical diagnosis of intussusception is entertained. This procedure must not be employed casually on the assumption that a condition that can be cured by an enema does not necessitate the same careful attention as does a disorder requiring an operation. To assure optimum results at minimum risk there must be complete co-operation between the attending physician, surgeon, and radiologist.

If the history, physical findings, and laboratory studies support a tentative diagnosis of intussusception and there are no contraindications to a barium enema, the patient is sent to the radiology department for chest and abdominal roentgenograms. If these films rule out another obvious cause for the abdominal findings, a barium enema is performed after first correcting any existing fluid or electrolyte deficiencies, and after alerting the operating room to prepare for surgical intervention should attempted hydrostatic reduction prove unsuccessful. Sedation administered prior to the performance of the barium enema will relax the patient and significantly increase the likelihood of successful hydrostatic reduction. I have found that intravenous Valium or an intramuscular combination of a short acting barbituate and meperidine are effective in rendering the procedure tolerable both to the child and to the attending radiologist.

A large caliber unlubricated retention catheter (22-26 French) capable of transmitting an adequate hydrostatic pressure is inserted into the rectum and the buttocks are taped together to prevent expulsion of the catheter. The balloon is then inflated under fluoroscopy sufficiently to ensure its retention. The barium container is then positioned three to four feet above the table top and the colon is filled under intermittent fluoroscopic observation, preferably with videotape recording. If an intussusceptum is encountered and moves retrograde in advance of the barium column, the enema is continued until successful reduction has been achieved. Several feet of terminal ileum must be filled to exclude a concomitant and persistent ileoileal intussusception. An edematous ileocecal valve cannot be distinguished from an incompletely reduced intussusception and unless there is retrograde filling of the distal ileum surgery must be performed. A post-evacuation film is always obtained following reduction to be certain that a recurrence has not occurred—in this event, the procedure is repeated. If three attempts of approximately five minutes

each (including supine and prone positioning) are unsuccessful in reducing the intussusception, the examination is discontinued, and the child is taken to the operating room. In our experience successful hydrostatic reduction of intussusception is possible in over 80% of infants and children.

Recurrent intussusception occurs in approximately 5% of children following either hydrostatic or surgical reduction, most frequently within 48 hours. Hence it is wise to admit the child to hospital for 24-48 hours following successful reduction. If symptoms recur during this period, the barium enema is repeated or surgical reduction is performed. If no recurrent symptoms develop, the infant can then be sent home with the parental admonition to return immediately if symptoms recur.

There are several advantages of carefully and properly applied hydrostatic reduction of intussusception over surgical reduction. In addition to being a simple procedure which shortens the duration of hospitalization, hydrostatic reduction avoids the significant incidence of late mechanical intestinal obstruction due to post-surgical adhesions.[6] Successful hydrostatic reduction should also decrease the number of resections required, since resections are sometimes performed on bowel which is mistakenly felt to be non-viable.[6] Even partial reduction of an intussusception to the cecum is helpful, since only a small localized incision is then necessary rather than a larger incision over a more distally located intussusception.

Summary

The current clinical and roentgenological aspects of intussusception in infancy and childhood have been presented. In addition, several of the common fallacies which have denied many infants the benefits of early radiographic diagnosis and prompt hydrostatic reduction, have been discussed, slain, and hopefully buried. The early clinical diagnosis of intussusception is often difficult and will be achieved more frequently if the attending physician and radiologist remember two principles. First, they must maintain a high index of suspicion for intussusception in any child with abdominal pain, despite equivocal and plain film findings. Secondly, the involved physicians must develop an "enematize not philosophize" attitude in any infant or child with possible intussusception. It is preferable to perform a negative barium enema in the child with abdominal pain, vomiting and bloody stools secondary to gastro-enteritis than to risk missing or delaying the diagnosis of a primary or co-existent intussusception. Few experiences in radiology are as personally satisfying as that of witnessing the sudden transformation of a tense, desperately ill infant into a relaxed, contented baby following successful hydrostatic reduction of an intussusception.

Acknowledgment

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Annual Meeting

The Minnesota State Medical Association's annual meeting in St. Paul, May 21-23, 1975, at the St. Paul Hilton Hotel.

Voiding Cystourethrography

Recent Advances

SHASHIKANT M. SANE, M.D.* and ROBERT A. WORSING, JR.†

Voiding cystourethrography is essential for satisfactory evaluation of the lower urinary tract. VCU is safe and does not require any anesthesia or preparation. Specific recommendations are made regarding the equipment and the radiation factors in order to reduce dramatically the diagnostic radiation doses in children.

DRAMATIC CHANGES have occurred in the methods of examination of the urinary tract in children in the last 15 years. Most Pediatric Radiologists believe that evaluation of the urinary tract is incomplete without a cystourethrogram. Voiding cystourethrography (VCU) and excretory urography (IVP) are supplementary examinations and when combined yield more positive information than any other single urologic investigation. The increase in VCU's is as resounding as the decrease in retrograde pyelography. Improvements in IVP's and VCU's have resulted in recourse to retrograde pyelography only in those rare instances where the collecting systems are not adequately visualized by IVP's or reflux from VCU's.

The first known report of positive contrast cystography was by Wulff[7] (1905). He utilized a 10% aqueous solution of bismuth subnitrate suspended by starch as the contrast medium, while demonstrating a septate urinary bladder. The same report mentions Keller, who radiographically demonstrated a bladder diverticulum by injection of air in the urinary bladder (1904). Cunningham[1] used Argyrol 50% while reporting the first retrograde contrast urethrography, (1910). Voiding cystourethrography was first mentioned by Glingar (1921).[2] Ortmann and Christiansen (1934)[3] described "follow through" urethrogram following IVP. The first credit of cine cystourethrography is given to Pachecho and deCosta by Pereira[4] in 1944. The most recent development in the pediatric urological field has been an attempt to simplify the technique and to reduce the amount of diagnostic radiation, particularly to the gonadal area.

*Director of Radiology, Minneapolis Children's Health Center, Minneapolis.
†Medical Student, University of Minnesota, Minneapolis.

Material

Two thousand, two hundred and seven urologic examinations were performed at Minneapolis Children's Health Center in the first 15 months since inception. Eight hundred and twenty-seven (37.5%) of these were VCU's, eleven hundred and four (50%) were IVP's, and two hundred and seventy-six (12.5%) of these were cystograms in O.R., and/or retrograde pyelograms. More than 60% of the retrograde pyelograms were performed by a single senior Urologist who still strongly believes that this is by far the best way to evaluate the upper urinary tract. Nineteen percent of cystograms in O.R. were performed on patients with exstrophy of urinary bladder. Recently the majority of the patients with exstrophy of the urinary bladder are being evaluated by voiding cystourethrography.

Three hundred and four voiding cystourethrograms were abnormal (36.8%) whereas in five hundred and twenty-three patients (63.2%) the findings were normal. Three hundred of these patients were boys (36.3%) whereas five hundred and twenty-seven of these were girls (63.7%). Three patients had ambiguous genitalia. The age distribution amongst the boys and girls is demonstrated in Table 1. There was a gradual increase in the number of examinations since birth to ten years, though the percentage yield of positive radiographic findings was inversely propor-

TABLE 1
Voiding Cystourethrograms
Age and Sex Distribution

Age (Years)	Males	Females	Total
0-1	23	28	51
1-3	40	111	151
3-5	75	157	232
5-10	126	156	282
Over 10	36	75	111
	300	527	827

tional to the age of the patient.

Indications

About two-thirds of the patients had voiding cystourethrography for possible infection of the urinary tract. Enuresis, neurogenic disease, anomalies such as exstrophy of the urinary bladder, imperforate anus, and miscellaneous conditions such as abdominal masses, trauma, abdominal pain, constipation, glomerulo-nephritis, hypertension, fever of undetermined origin, and failure to thrive, were the primary indications in the remaining one-third of the patients.

There is no completely satisfactory answer to the question of when a child with possible urinary tract infection should be referred for uroradiologic examination. We feel that those children who do not respond to medical management and those children who have two or more urinary tract infections—regardless of their sex—should have a complete uroradiologic examination which must include both the voiding cystourethrography and excretory urography.

Recording Methods

The entire voiding cystourethrography is recorded on video tape recorder (Ampex VTR 5800) and the pertinent photographs of the images on the output phosphor of the image intensifier is made with a rapid sequence 105 mm. camera. These 105 mm. spot films are of the same size as the conventional spot films and are as effective in detecting the vesicoureteral reflux and demonstrating the pathological anatomy and physiology of the urinary bladder and the urinary tract.

We utilize Plumbicon (lead oxide Videcon) as the camera pick-up tube. Target material used is lead monoxide which leads to some unique advantages, particularly for the fluoroscopic examination in children. The Plumbicon tube has much higher contrast than the standard Videcon and is ideally placed for fluoroscopy in children at low radiation levels because of its maximum sensitivity characteristics. The freedom from lag—unlike Videcon—makes it highly effective when evaluating rapid body functions such as voiding cystourethrograms. In order to make the Plumbicon camera tube effective one must have a brightness stabilization system attached to the fluoroscopic unit as well as a kV stabilizer.

The milleamperage and kilovoltage used during the fluoroscopy and radiography varies with the age and the size of the patient. Usually for the children under the age of six years, fluoroscopy is performed at or below .2 mA and 70 kVp level and the 105 mm. photo-timed spot films are obtained at 80 kVp. For the children older than six years of age, the fluoroscopy is performed between .2 and .4 mA level depending on their size, and between 70 and 80 kVp's are used for fluoroscopy. The 105 mm. photo-timed spots then are obtained at 90 kVp's.

Main reasons for using these factors during fluoroscopy and radiography is to slash the radiation levels given to the child during the examination (Figure 1). There is no question about the fact that the fluoroscopic image would be technically better and clearer to the radiologist's eyes if we did use higher mA during fluoroscopy. However, with a little training and patience, one can

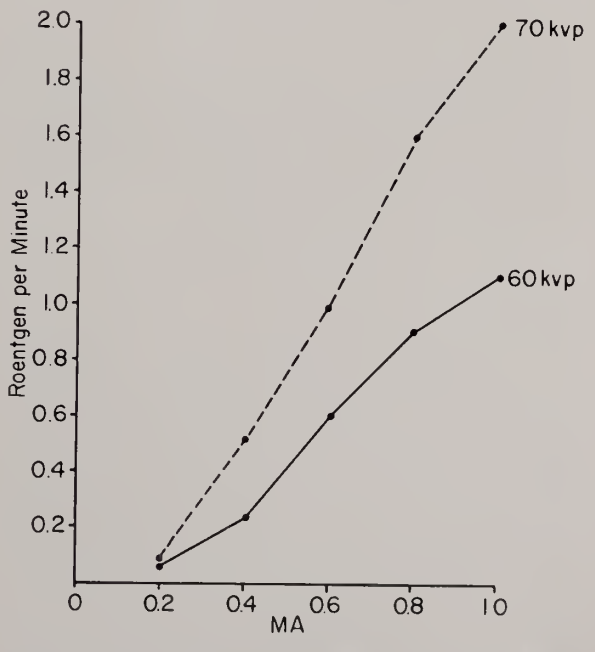


Fig. 1—Fluoroscopic mA value is plotted against amount of radiation at the table top. If the fluoroscopy is done at .2 mA, the radiation output at the table top is at 62 mR/minute in comparison to 2,000 mR/minute if fluoroscopy is done at 1 mA level.

easily get accustomed to examining the children at these low radiation factors without missing any findings while significantly decreasing the body and gonadal radiation dose to the child. Another major advantage of utilizing 105 mm. spot films over the conventional spot films is to reduce dramatically (11 times) the amount of radiation per exposure during radiography (Figure 2), while maintaining the high diagnostic potential of the conventional spot films.

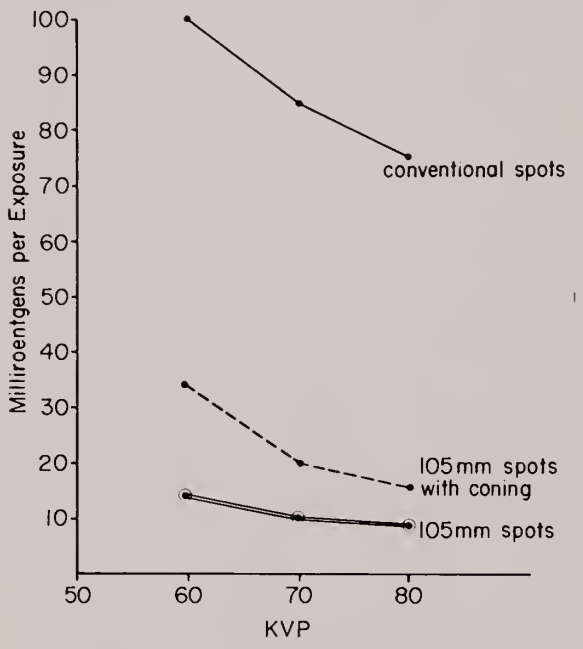


Fig. 2—The conventional spot films give between 100 to 80 mR/exposure depending upon the amount of kVp's used. The amount of radiation from exposure for 105 mm. spot films in the same range extends between 9 to 14 mR/exposure thus reducing the radiation dose by nine to eleven times per exposure.

Technique

Preparation of the Patient

As a routine we do not prepare the children with laxatives, low residual diet, or overnight fasting for VCU. They are NPO at least for three hours prior to the examination only if VCU is to be followed by IVP. Prior to the VCU, both the x-ray technologist and the roentgenologist explain the entire technique to the child individually in simple language and try to make the child fairly conversant with the equipment as well as the procedure. We encourage the parents to be present when the examinations are being performed. In our opinion, their presence in most instances makes the examination easier to accomplish and obtain satisfactory results. No anesthetic is used for voiding cystourethrography and the examination is avoided if a recent instrumentation such as cystoscopy has been performed within the last 24 hours.

Immobilization

We do not immobilize the children if we possibly can avoid it. Under the age of two years, when it is difficult to communicate satisfactorily with the child so as to place him/her in a relaxed state of mind and body, we use elastic ace bandages and wrap the lower extremities together. The upper extremities are immobilized by raising the hands above the level of the shoulders and immobilizing them by stockinettes. We find that these simple devices are as effective as and less uncomfortable than the highly publicized "brat-board."

Instrument Trays and Contrast Media

The cost of the sterilization procedure in the hospital is so prohibitive these days, that a ready made cystography tray appears to be the most efficient and relatively inexpensive way to obtain a sterile catheterization technique. We utilize Bard catheter trays which supply all the necessary equipment including the cleansing solution, (Benzalkonium Chloride solution, 1:750). For girls we utilize Bardex catheters size eight through fourteen and for boys we use Bardic feeding tubes from size three to eight. Sodium diatrizoate and Meglumine diatrizoate are the safest media for cystourethrography. Though occasionally pain, urgency, and urethral spasm have been reported with these contrast media, in the literature as well as in our series (2%), these symptoms conceivably could be secondary to recent catheterization instead. We commonly employ 25% weight by volume sterile aqueous solution of sodium diatrizoate or 30% weight by volume sterile aqueous solution of Meglumine diatrizoate in 300 cc. intravenous infusion sets.

Procedure

The child empties the urinary bladder prior to the examination. After catheterization of the child with the sterile technique, the residual urine volume is measured and in many instances these urine samples are sent to the laboratory for urinalysis and for culture examinations. The contrast medium is injected into the urinary bladder by the gravity method from a height of 50 cm. above the table top, this being the upper limit of normal

voiding pressure. At frequent intervals the urinary bladder, the vesical, the retrovesical, and the renal areas are fluoroscoped for any evidence of vesicoureteral reflux, bladder trabeculations and/or diverticula, or any other abnormalities. The voiding phase is studied by fluoroscopy and documented on video tape and by a 105 mm. camera with sequential films obtained at one per second during early, mid, and late phases of voiding. This examination is performed in steep oblique position (either standing or lying down position) in boys and in lateral position for girls, preferably sitting on a small potty chair specifically prepared for this purpose (Figure 3). The only consistent method to initiate the voiding mechanism is to make sure that the urinary bladder is distended to i s maximum capacity. At the end of micturation 105 mm. spot films of the pelvis and the renal area are obtained. If the child is unable to void completely under observation, a single abdominal film following the voiding on the commode is obtained.



Fig. 3—Use of specially made potty chair to evaluate the bladder and urethral function, which is done best in lateral position.

Normal Findings

The base plate is a structure situated in the floor of the urinary bladder that affects the appearance of the cystourethrogram. It completely surrounds the internal urethral orifice which is located slightly anterior to its center. Most of the posterior part of the base plate consists of the trigone (mesodermal in origin) whereas the anterior and lateral parts are made up of fundus ring (endodermal in origin). In its normal relaxed position this anatomic and functional unit, base plate, is flat and located either on or just above the pubosacral line. In this position the tone of the concentrically arranged circular smooth muscle fibers closes the internal urethral orifice and prevents voiding. The base plate has to be forced out of its normal flat position into the cone formation in order to initiate voiding. Once this has happened, continued contraction of the muscle in the fundus ring carries the funnel formation to completion and voiding takes place. Contraction of the smooth muscle progressively raises the adjacent walls of the base plate towards each other. The shortening of the contracting smooth muscle fibers pulls and elevates the walls until they become vertical and parallel near the end of voiding and create the trigonal canal. It is this trigonal canal in its various stages of development which affects the appearance of the urethrogram. In addition, fusion of smooth and striated muscle (inter muscular incisura), levator ani sling, sphincter compressae urethrae muscle and a collagenous nonmuscular distal urethral segment effect and determine the normal urethrographic appearance.

Tremendous variations occur in the normal urethrogram and the three factors[6]—the position of the trigonal plates, urethral width, and urethral configuration—are responsible for them. The vast degree of normal variation emphasizes the importance of sequential spot films to visualize the urethra throughout the voiding cycle initial, mid, and late.

It has been observed that considerable variation occurs in the bladder neck diameter during the different stages of voiding and that direct proportional relationship exists between it and the urethral diameter. The bladder neck diameter is smallest during early and late voiding whereas it is the largest when the urethra is maximally distended. Thus, a bladder neck diameter is a physiologic manifestation of the position of the trigonal plate and the degree of urethral distention, and one should be extremely careful in diagnosing pathologic bladder contracture. True bladder neck contracture only exists when the trigonal plates are oblique to form a shoulder above and when the urethra is distended wider than the bladder neck to form a shoulder below with these findings persisting through the entire act of voiding.[5]

Factors determining the degree of urethral

width attained during the act of voiding are not completely understood but the intramural tension, intralumenal volume and velocity of flow are some of the important factors. Widest urethras seen in normal children are seen in those children who void without hesitancy and with a large volume high velocity strength. Direct calibration of the urethra is a much more reliable means of establishing the exact urethral width.

Similar variations occur in the diameter of the meatus and the distal urethral segment during various stages of voiding. As in the case of the bladder neck, their diameters are smallest during early and late voiding, whereas they are largest during the full voiding when there is large volume and high velocity strength.

Abnormal Findings

Three hundred and four patients showed one or more abnormal findings on voiding cystourethrograms (36.8%) whereas five hundred and twenty-three patients showed normal findings (63.2%). Abnormal findings identified on voiding cystourethrograms are shown in Table 2. The most frequent abnormal finding was that of vesicoureteral reflux (Figures 4-8). This reflux was observed in two hundred and twenty-two (72.4%) and when observed the following aspects of the reflux were carefully evaluated.

1. Time of occurrence. Whether it occurred during the early or late phase of filling, or during the phase of voiding. Presence of a massive reflux during the early phases of filling may represent a wide gaping ureteral orifice on that side and may carry a poor prognostic significance, whereas a small reflux only during the phases of voiding is of less importance.

2. Partial or complete. The significance of a massive or complete reflux is greater than a small partial vesicoureteral reflux. If the reflux is complete, the presence or absence of duplication or dilatation or deformity of the upper collecting system are carefully evaluated.

3. Transient or persistent. Transient partial vesicoureteral reflux may represent temporary alteration in physiology to a stimulus such as infection, whereas a persistent massive reflux



Fig. 4—Paraureteral Hutch diverticulum (D) demonstrated only during the phase of voiding. Surgical correction with reinsertion of the ureter into the urinary bladder through a new oblique canal is required for elimination of the urinary signs and symptoms.

TABLE 2

Voiding Cystourethrograms

Number of Examinations:	827	
Normals:	523	63.2%
Abnormals:	304	36.8%

Abnormal Findings on Voiding Cystourethrograms

Frequent findings	Number	Percentage
Vesicoureteral reflux	220	72.4
Trabeculations of the bladder	58	19.1
Bladder diverticula	54	17.8
Hutch diverticula	9	3.0
Exstrophy of bladder	36	11.8
Meatal stenosis	28	9.0
Urethral stricture	12	4.0

Infrequent Findings

Neurogenic bladder	9	Rectourethral fistula	3
Bladder neck thickening	8	Posterior urethral valves	3
Urachal remnant-cyst-sinus	5	Duplication of urethra	2
Ectopic ureter	3	Urethral diverticula	3
Hypospadius	8	Genital rhabdomyosarcoma	2
Epispadius	3	Ovarian cysts and dermoids	3

Reflux in prostatic duct or Vas deferens 6

probably represents altered anatomy as well.

4. Unilateral or bilateral.

5. Ureteral peristalsis and emptying. Peristaltic activity of the ureter is evaluated by fluoroscopy and documented by video tape. The approximate time for the ureteral reflux to empty completely in the urinary bladder is noted. Active ureteral peristalsis with rapid emptying of the reflux has better prognosis than a massively dilated ureter which shows prolonged retention of the reflux contrast medium and which shows an unsynchronized to-and-fro and ineffectual peristaltic activity.

Fifty-eight patients (19.1%) showed mild to severe form of bladder trabeculations with cellule and saccule formation. This is probably a result of obstruction at the bladder neck or distal to it



Fig. 5—A huge urachal remnant (R) extending from the fundus of the urinary bladder all the way up to the level of the umbilicus anteriorly. Note complete reflux in both upper collecting systems. Note reflux into Vas deferens bilaterally (arrow).



Fig. 6—Neurogenic bladder. Urinary bladder is cone-shaped, trabeculated, and appears small in size. Note bilateral ureteral reflux.



Fig. 7—Posterior urethral valve Type I (arrow). Note the massive dilatation of the posterior urethra (P) in contrast to normal caliber distal to the site of the posterior urethral valve. Note reflux in the massively dilated ureters (U).



Fig. 8—Vaginal rhabdomyosarcoma. Note irregular filling defects on the anterior vaginal wall (arrows). This reflux of contrast medium in the vagina is achieved during the voiding phase of cystourethrogram. Note ureteral reflux.

or secondary to chronic lower urinary tract infection. In fifty-four patients (17.8%) bladder diverticula were observed. They represent outpouching or herniation of the bladder mucosa and submucosa between interlacing bundles of muscle which is frequently hypertrophic. It is possible that the production and distention of the diverticula may protect the kidney from severe back pressure. The openings of the diverticula occur most frequently at the base and the lower halves of the lateral walls of the bladder. A common site of diverticula has been adjacent to ureterovesicular junction. The incorporation of this junction in the diverticulum has been occasionally recognized. Hutch suggested that many of these diverticula are a consequence of congenital or acquired deficiencies of the muscular structures surrounding the oblique canal through which the ureter enters the bladder. Occasionally they fill only during the phase of voiding (Figure 4). Their significance lies in the fact that surgical correction with reinsertion of the ureter into the urinary bladder through a new oblique canal is required for elimination of the urinary signs and symptoms related to such a diverticulum and the reflux commonly associated with it. We saw only nine such instances of Hutch diverticula (3%).

Exstrophy of the urinary bladder was observed in 36 patients (11.8%). It is important to evaluate size, tone, trabeculations, or septation of the urinary bladder. More important is to evaluate the function of the bladder neck and the available segment of the urethra. There is frequent association of ureteral reflux.

Five patients showed huge urachal remnants (Figure 5). In one instance it was associated with a small urachal cyst and in one instance a small sinus tract drained at the umbilicus. Neurogenic bladder was observed in nine patients. Figure 6 demonstrates one such classical example where a markedly trabeculated cone-shaped urinary bladder is observed. Normal sphincter mechanism at the ureterovesical junction tends to be absent with associated vesicoureteral reflux. Bladder neck thickening was observed in eight patients, whereas in three cases ovarian cysts such as dermoids were diagnosed during voiding cystourethrography.

Posterior urethral valves were present in three patients (Figure 7). All these three patients had Type I posterior urethral valves as classified by Young in 1919.[8] The three types are:

Type I—valves passing from the distal end of the verumontanum to the lateral urethral wall

Type II—valves forming partial or complete diaphragms arising

a. proximal to the verumontanum
b. distal to the verumontanum
c. at the verumontanum and passing laterally to the walls of the urethra

Type III—valves arising from the proximal end of the verumontanum and passing upwards to the bladder outlet. This type of valve usually consists of low ridges and is non-obstructive in type.

Voiding cystourethrography is by far the only means of diagnosing the posterior urethral valve radiographically. During retrograde urethrograms these membranous folds forming urethral valves get easily displayed laterally and no evidence of obstruction can be recognized. Occasionally they are difficult to be identified during urethroscopy as well.



Fig. 9—Meatal stenosis. Note massive dilatation of the entire urethra with pinpoint meatal opening. Also note splaying of the contrast medium distal to the pinpoint meatus.

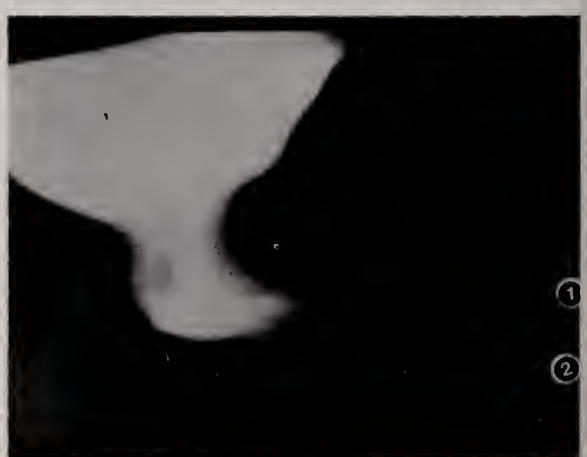


Fig. 10—Duplication of urethra. Upper urethral channel shows a small diverticulum. The upper accessory urethral channel (1) was surgically excised.

Two patients showed duplication of the urethra and in three cases urethral diverticula were observed (Figure 10). Eight patients had hypospadias, whereas three patients had epispadias. In three instances ectopic ureteral openings in the posterior urethra were observed. Three patients showed rectourethral fistula, whereas in six instances reflux of contrast medium in the prostatic duct or Vas deferens was observed (Figure 5). Two patients showed a vaginal rhabdomyosarcoma (Figure 8.)

In 28 instances (9%) meatal stenosis was seen, whereas in 12 instances (4%) urethral stricture was observed. Figure 9 shows a classical example of meatal stenosis with massive dilatation of the entire urethra with splaying of the contrast medium just distal to the meatal opening.

Other significant associated anomalies in the patients who underwent voiding cystourethrograms were as follows: 14 patients showed spina bifida, whereas five patients had meningomyelocele. Sacral and vertebral abnormalities such as hypoplasia and hemivertebrae were observed in 15 patients. Two patients showed changes of Legg-Calve-Perthes disease which were clinically unsuspected and five patients showed dislocation at the hip joints. One patient had prune-belly syndrome.

Summary

1. Voiding cystourethrography is an extremely important examination for evaluation of the anatomy, physiology, and pathology of the lower urinary tract. VCU is safe, efficient, and does not require any anesthetic drugs. No preparation is necessary for VCU. Simple immobilization devices should be used, only when necessary.

2. The VCU should be performed with low levels of mA during fluoroscopy and the voiding phase should be recorded sequentially on the video tape and on 105 mm. spot films with the help of a rapid sequence camera. These modifications reduce the dose of radiation given to the child significantly and does not sacrifice any diagnostic capability of VCU. Plumbicon tube, because of high contrast, maximum sensitivity and freedom from lag is an ideal pick up tube for fluoroscopy in children.

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Hodgkin's Disease

Historical Perspective and Current Radiotherapeutic Management at University of Minnesota

DAVID G. SMITH, M.D.,* THOMAS K. JONES, M.D.† and SEYMOUR H. LEVITT, M.D.‡

A historical documentation of significant developments in the diagnosis and treatment of Hodgkin's disease is presented. This is followed by a description of the current radiotherapeutic management of this disease in use at the University of Minnesota.

HODGKIN'S DISEASE represents a neoplastic process in which remarkable recent progress has been made in curability as well as increased survival time as a result of treatment.

Although at once thought to be a disease leading inexorably to fatal outcome this view has been largely dispelled in light of published reports of long survival in significant numbers of patients.[1-3] Justifiably, we can state that the control we now experience over this disease has come largely through the efforts of radiotherapists working towards improvement in application of their art. Only through the more knowledgeable and aggressive use of irradiation in the treatment of Hodgkin's disease, has the possibility of cure become a reality to the majority of patients so afflicted.

We will review the historical points of interest in this disease and discuss the current radiotherapeutic management of Hodgkin's disease at the University of Minnesota.

Historical

Pathology

Although some of Thomas Hodgkin's original patients were later found to have diseases other than the one for which he is so well known, his is rightly regarded as one of the earliest reports of this disease.[4] Langhans (1872) & Greenfield (1878) were the first to describe histopathological findings in this disease, later expanded upon with definitive reports by Sternberg (1898) and Dorothy Reed (1902), whose names have become associated with the classical diagnostic cell in Hodgkin's disease.[5]

Jackson & Parker contributed significantly by classifying Hodgkin's disease on the basis of histologieal findings.[6] The delineation of paragranuloma, granuloma, and sarcoma types became the standard nomenclature for many years.

Lukes et al. in 1963 and 1966 presented a modified histopathologie classification which described six categories:[7,8]

(a) lymphocytic and/or histiocytic nodular,
(b) lymphocytic and/or histiocytic, diffuse,
(c) nodular sclerosis,
(d) mixed,
(e) diffuse fibrosis and
(f) reticular.

This classification was based on the findings of an inverse relationship between the number of lymphocytes and the number of Reed-Sternberg cells in a given section.

At the Rye, N.Y. Conference on Hodgkin's disease in 1965 the histopathologie classification of Lukes et al. was reduced to four categories:

Lymphocyte predominence (LP)
Nodular sclerosis (NS)
Mixed cellularity (Mixed)
Lymphocyte depletion (LD)

These histological types were found to correlate with prognosis, LP having the best prognosis, NS

*Assistant Professor, Department of Therapeutic Radiology, University of Minnesota Medical School; Junior Faculty Clinical Fellow, American Cancer Society, Minneapolis.
†Associate Professor, Department of Therapeutic Radiology, University of Minnesota Medical School, Minneapolis.
‡Professor and Head, Department of Therapeutic Radiology, University of Minnesota Medical School, Minneapolis.

next best, then mixed cellularity and LD having poorest prognosis.[5]

Staging

In 1950, Peters introduced a three-stage system of clinical classification of extent of disease, a concept which added significantly to the understanding of Hodgkin's disease.[1]

Kinmonth in 1952 introduced lymphangiography which greatly facilitated evaluation of intra-abdominal disease, an area which[10] had heretofore been an unknown in the staging of a patient's disease.

With the development of lymphangiography and other modern diagnostic aids which permitted better definition between localized and widespread disease, the Rye, N.Y. Conference on Hodgkin's disease in 1965 expanded the three-stage classification of Peters to a four-stage classification as proposed by Kaplan in 1964.[5]

Clinical symptoms, designated B (i.e. fever, night sweats, pruritus, weight loss—as originally proposed by Peters & Middlemiss) or lack of symptoms, designated A, were to be applied to all stages.

In 1969, 1970, staging laparotomy with biopsy of periaortic nodes and liver, open bone marrow biopsy, and splenectomy was found to be valuable in detecting unsuspected abdominal disease.[11-13] Involvement of spleen of normal size and weight with Hodgkin's disease was and is the most striking fact from laparotomy data. In 117 previously untreated patients at Stanford, 44 of 117 had splenic involvement at laparotomy. Also bone marrow *biopsy* was found to be necessary to establish disease in the marrow since Hodgkin's disease is focal in nature and therefore a single aspiration is not useful. A biopsy with cutting needle such as Westerman-Jensen or open biopsy at time of laparotomy[5] was found to be required to establish the presence or absence of bone marrow involvement.

As a result of the new information obtained from laparotomy data the Ann Arbor Conference on Hodgkin's disease in 1971 established staging of disease based on the clinical stage of disease (CS) and pathologic stage (PS). In this staging system. the patient has a careful clinical evaluation followed by staging laparotomy, splenectomy, open liver biopsy, open bone marrow biopsy or other additional tissue biopsies.[5] In this staging system if no additional information is found at laparotomy, then CS = PS.

However, in a case in which a patient (without constitutional symptoms) is thought to be Stage II on basis of initial examination and workup but after laparotomy is found to be Stage III, on basis of involved spleen, the designation for this patient would be:

CSIIA, PSIIIA S+, H−, N−, M−

Where symbols S = spleen, H = liver (hepar) N = periaortic nodes, M = open marrow biopsy.

This type of classification is necessary in order to compare cases of similar extent of disease and diagnostic evaluation.

In addition, the Ann Arbor Conference called attention to those cases classified previously as Stage IV in which there was only limited extralymphatic involvement as opposed to the Stage IV disease with extensive extralymphatic involvement. In some of the cases with minimal extralymphatic involvement the prognosis was the same as similarly localized disease confined to the lymphatic system. To this type of disease the suffix "E" is attached to denote minimal extralymphatic involvement. Examples of "E" involvement include multiple nodules limited to one lobe of lung, direct

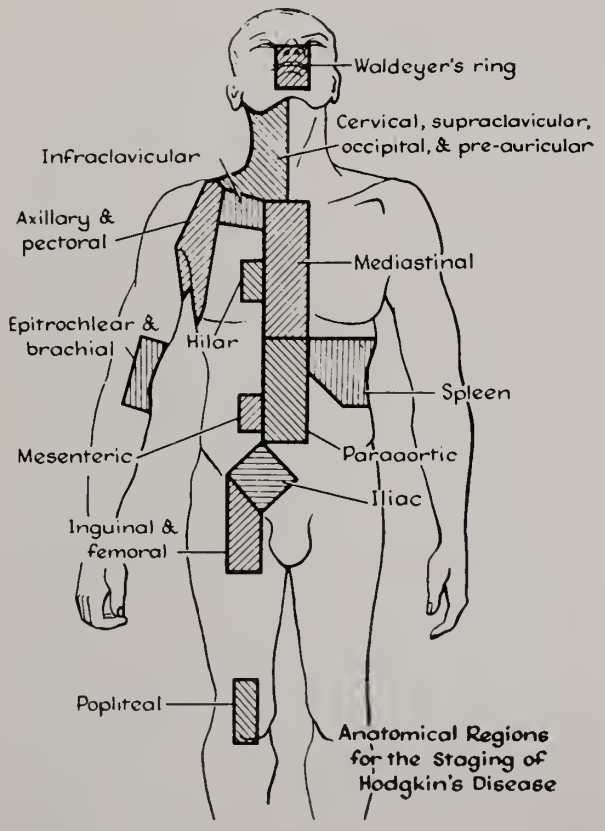


Fig. 1—Definition of anatomic lymph node regions adopted for staging purposes at the Rye, N.Y. Symposium on Hodgkin's disease.

invasion of lung associated with mediastinal and/or ipsilateral hilar adenopathy, or unilateral pleural effusion.

The Ann Arbor Staging Classification:

Stage I—Involvement of single lymph node region (I) (Figure 1) or of a single extralymphatic organ or site (IE).

Stage II—Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site and of one or more lymph node regions on the same side of the diaphragm (IIE).

Stage III—Involvement of lymph node regions on both sides of the diaphragm (III) which also may be accompanied by involvement of the spleen (IIIS) or by localized involvement of an extralymphatic organ or site (IIIE) or both (IIISE).

Stage IV—Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement.

Treatment

Irradiation was first used by Pusey in the treatment of this disease in 1902.[5]

Initial attempts at treating Hodgkin's disease consisted of administration of sub-tumoricidal doses of irradiation to localized areas of clinical involvement. Most often this was followed by recrudescence of disease in adjacent or previously treated areas.

Gilbert must be accorded significant recognition as one of the first radiotherapists to document the need for aggressive treatment in Hodgkin's disease based on his observations of the orderly progression of this disease from the site of clinical involvement to the next adjacent lymph node area.[15]

Peters contributed significantly in advocating treatment of adjacent, clinically uninvolved areas in addition to the involved areas. The better treatment results with this more aggressive approach led logically to the "total nodal" treatment plan in which all principal lymph node regions are irradiated sequentially, as advocated by Kaplan and others.[5]

The chemotherapeutic approach to this disease began in the 1940's with reports of temporary regression of disease. More recently multiple drug regimens have been found to produce long-lasting remissions in advanced Hodgkin's disease. Nevertheless, radiotherapy remains the major therapeutic modality in the curative approach to this disease and is assuredly so in early disease (Stage I & II).

Treatment—General Considerations

"Hodgkin's disease is a cruel and ruthless adversary, which seldom permits the physician to commit an error in judgment without serious consequences to his patient."—Henry S. Kaplan.[5]

The first treatment a patient with Hodgkin's disease receives is the best chance for cure. Studies show that patients who relapse after primary treatment are much more likely to die of Hodgkin's disease than those who have not relapsed.[16] Proceeding to treatment of a local field of irradiation or commencement of single drug chemotherapy before the full extent of the patient's disease is known is therefore inviting failure of treatment. Procrastinating in biopsy of suspicious nodes in favor of prolonged observation or antibiotic therapy provides the disease process greater time to spread, and thereby reduces chances of cure.

Initiation of chemotherapy without a trial of radiotherapy in the earlier stages of Hodgkin's disease is not defensible in view of the fact that irradiation remains the single curative agent in this disease.

Radiotherapeutic Management of Hodgkin's Disease at University of Minnesota

Following referral of a patient with suspected Hodgkin's disease to the Department of Therapeutic Radiology, a thorough review of all available information is initiated. A complete history and physical examination is, of course, of primary importance.

Pertinent x-ray and laboratory studies are obtained including chest Xray, complete blood count, sedimentation rate, urinalysis and battery of blood chemistries—SGOT, BUN, creatinine, calcium, alkaline phosphatase, electrolytes, serum electrophoresis. Outside slides of biopsy material are reviewed to confirm diagnosis and histological type of Hodgkin's disease. If patient has not been diagnosed, appropriate biopsy material is obtained. If diagnosis of Hodgkin's disease is confirmed further studies are obtained including intravenous pyelogram, lymphangiogram and bone marrow biopsy. Other studies are obtained as indicated by patients' symptoms and clinical signs.

At present, laparotomy is routinely recommended to the patient for evaluation of abdominal disease, unless the patient is found to be Stage IV by the previous evaluation.* Assuming the clinical situation is not urgent, radiotherapeutic treatment is not started until all necessary diagnostic information, including laparotomy, has been obtained.

Once the decision to proceed with irradiation treatment is made, the treatment planning process is as follows:

If the lymphatic regions above the diaphragm are to be irradiated first (the "mantle") as is usually the case, the patient is placed in treatment position and an x-ray film is exposed using the treatment machine as the energy source. (Currently a 10 MeV linear accelerator).

Lines are drawn on this film outlining the areas of lung which are to be shielded with lead blocks during the radiation treatments (Figure 2). Great care is used in constructing these lines since if disease is shielded by the lead block the patient's disease will undoubtedly recur after treatment. On the other hand, a maximal amount of lung tissue must be spared irradiation in order to prevent severe radiation pneumonitis and later pulmonary fibrosis and pulmonary insufficiency. Also as much heart as possible should be shielded to prevent pericardial and myocardial damage.

Next, using a special hot-wire cutting apparatus, a cutout is made in a styrofoam block corresponding to the areas of lung and heart we wish to shield (Figure 3).

This system permits duplication of the geometry of actual treatment conditions so that the walls of the cutout will diverge exactly as the x-ray beam will during the radiation treatment. This allows for a very "sharp" beam of radiation to be applied to the desired areas while simultaneously providing maximal protection to adjacent protected tissue.

The styrofoam block is then filled with a warm lead alloy which solidifies at room temperature.

The foregoing procedure is repeated exactly for treatment of the posterior "mantle" field, with the patient lying on the abdomen.

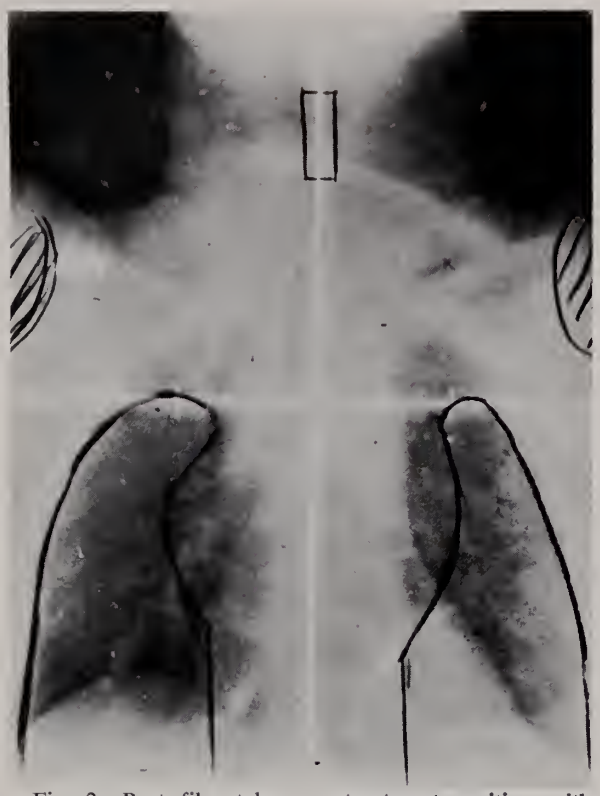


Fig. 2—Port film taken on treatment position with drawing outlining areas to be shielded with lead blocks.



Fig. 3—Hot-wire cutout of styrofoam block corresponding to outline drawn on port film.

*It is to be noted that laparotomy is not universally employed in the evaluation of a patient with Hodgkin's Disease. We are currently employing it in our evaluation so as to accurately assess abdominal involvement with Hodgkin's Disease, which data can be reliably obtained in no other way. Our treatment plan is directly related to the findings at laparotomy and consequently we feel it is an essential staging procedure.

If patients are to be treated in a uniform manner ie: "total nodal" irradiation, then we do not feel staging laparotomy should be routinely employed in the staging procedure.

During the treatment course anterior and posterior "mantle" treatments are alternated on successive days.

Figure 4 shows the lead block in place during treatment.

Figure 5 is port film with lead block in place.

Note the generous treatment margin given to the infraclavicular and hilar areas. Other than small lead shields placed over the humeral heads, lower lateral chest wall and larynx, all areas not covered by lead, as seen in this film, are irradiated to tumoricidal doses during the treatment course.

Following completion of treatment to the "mantle" field, the lower border of the field is tattooed for future reference. After a delay of approximately four weeks to allow recovery of blood counts and patient's general condition, the patient returns for irradiation to the infra-diaphragmatic lymphatic areas. The amount of tissue irradiated below the diaphragm is related to the extent and location of disease. In stages I & II with above—diaphragm disease presentation, only the periaortic nodes will be irradiated, extending

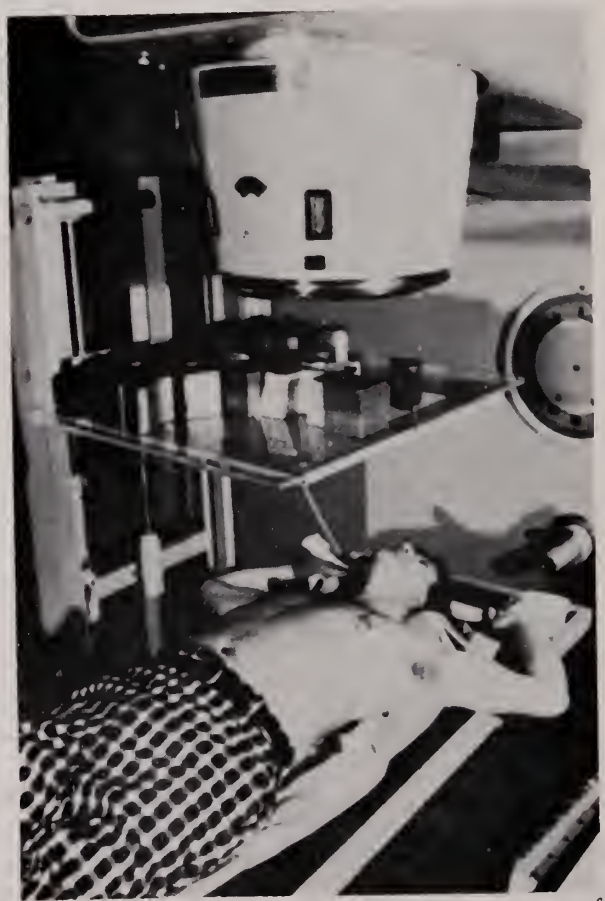


Fig. 4—Lead block in position during treatment of "mantle" field.



Fig. 5—Port film with lead block in proper position during treatment.

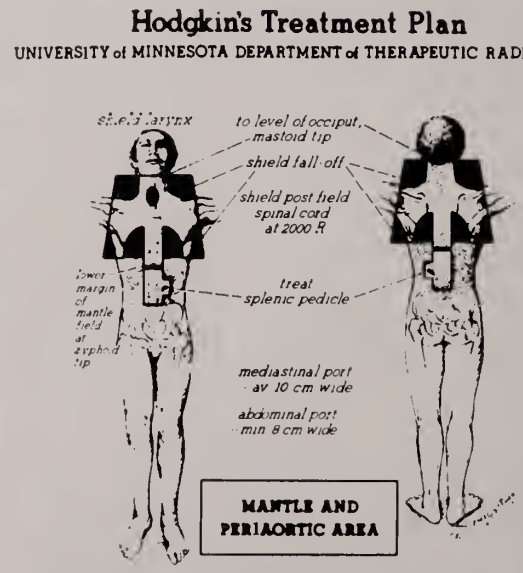


Fig. 6—Extent of area treated for Stage I & II presentations above diaphragm.

from the inferior margin of the mantle field to the bifurcation of the aorta (Figure 6). This plan of treatment is based on data of Rosenberg and Kaplan[14] describing frequent association between left low cervical-supraclavicular node involvement and periaortic node, spleen or splenic hilar nodes. In their series of patients this constituted the single most frequent extension of disease in patients treated with local or limited supradiaphragmatic radiotherapy.

In Stage III disease or cases in which below —diaphragm presentation is made the "inverted-Y" field is employed (Figure 7).

The total dose given to the "mantle" and infradiaphragmatic fields ranges from 4000-5000 rads delivered at 150 rads per day with the higher doses given to clinically involved areas and lower doses to "prophylactic" areas. The mantle field therefore requires six to seven weeks to complete, as does the infradiaphragmatic treatment. With the added four week rest between treatments the total course is approximately four months in length.

Because of the complexity involved in delivering a uniform dose of irradiation throughout the mantle field, we utilize a computer calculation of dose at six representative sites within the field. This necessitates lead blocking of appropriate sites as treatment course completion is reached in order to avoid overdosage at these sites.

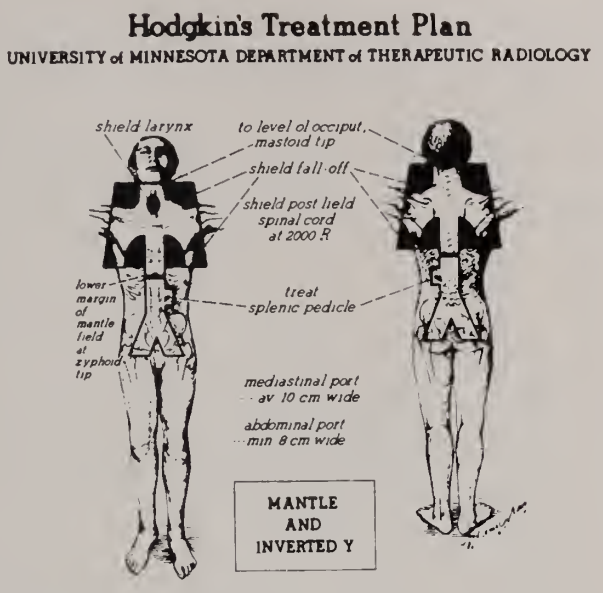


Fig. 7—Extent of area treated in Stage III disease.

Treatment Results and Prognosis

Kaplan, compiling data from several series of untreated Hodgkin's disease patients (1923-1955) reports an average five year survival of 7.5% and 10 yr of <1%[5] (Figure 8).

A similar collection of data from series treated with high dose kilovoltage radiotherapy produced five year survivals of 30-50% and 10 year figures of 20-30%.

A recent series of patients of all stages treated with intensive megavoltage radiotherapy at Stanford University shows a five year survival rate of 73.3%, 10 year figures not yet available.[5]

Treatment result data from University of Minnesota is in evaluation phase but early figures demonstrate results similar to these from Stanford. This data will be included in a subsequent publication.

This impressive improvement in survival reflects our better understanding of the Hodgkin's disease

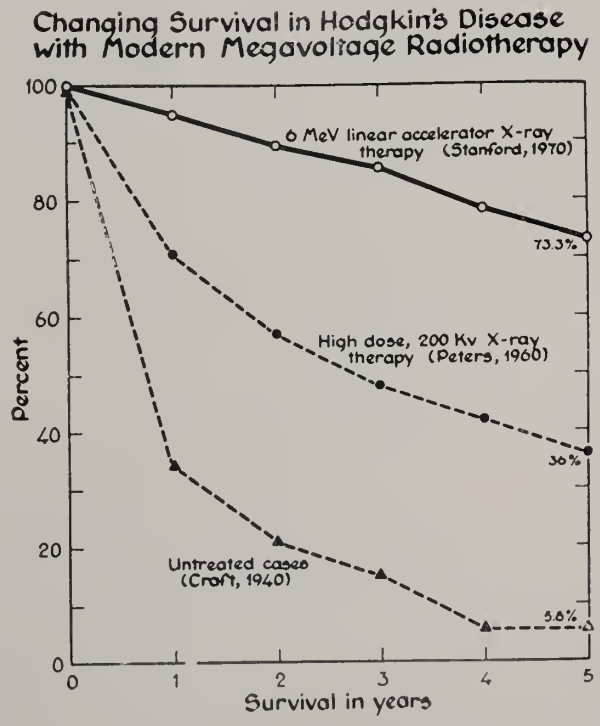


Fig. 8—Changing Survival of Hodgkin's disease.
(Reprinted with permission of Henry S. Kaplan and publisher from article "Hodgkin's disease and other malignant lymphomas. Calif Med 113:23-38, 1970).

process, improved radiation therapy equipment, techniques and personnel and the more intensive radiation doses given over larger segments of the lymphatic system.

At the present time, treatment of early Hodgkin's disease with irradiation is highly successful. Future improvement in treatment of more advaneed cases should be fortheoming through the combined uses of radiotherapy, chemotherapy, and the hoped-for eventual sueeess of immunotherapy. Great strides have been made in control of this onee-universally fatal disease. This can only help stimulate us to work for the ultimate elimination of Hodgkin's disease as a threat to life.

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Minnesota Society of Clinical Pathologists

Symposium on Endoerine Disorders

Date:	Saturday, April 5, 1975
Place:	Health Sciences Building, University of Minnesota
9:45-10:00 a.m.:	Welcome Address and Announcements—Charles Chedister, M.D., President
10:00-11:00 a.m.:	Histology of the Thyroid Gland in Normal and Abnormal Sta•es—Louis B. Woolner, M.D.
11:00-12:00 noon:	Thyroid Function Testing—Colum A. Gorman, M.D.
12:00- 1:30 p.m.:	Luncheon at Campus Club, Coffman Union
1:30- 2:00 p.m.:	Normal and Abnormal Histology of the Parathyroid Gland—Erhard Haus, M.D.
2:00- 2:30 p.m.:	Parathyroid Function Testing—Arnold Lindall, M.D., Ph.D.
2:30- 3:15 p.m.:	Adrenal Gland Function in Normal and Abnormal States—Richard Doe, M.D.
3:15- 3:45 p.m.:	Histology of the Adrenal Gland in Normal and Abnormal States—J. Aiden Carney, M.D.
4:15- 5:00 p.m.:	Endocrine Aspects of Hypertension—David M. Brown, M.D.
7:30 p.m.:	Commemorative E. T. Bell Banquet for friends of Dr. Bell and members of the Society, Marquette Inn
Tuition:	$10.00 (includes luncheon, lecture summaries, and booklet of 35 mm. slides; dinner additional)
Applications:	Before March 15 to: Wayne A. Chadbourn, M.D., Secretary, Minnesota Society of Clinical Pathologists, 900 South 8th Street, Minneapolis. Minnesota 55404
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^{67}Gallium Scanning

An Aid in Management of Neoplasias, Including Lymphoma

MARVIN E. GOLDBERG, M.D.*; RAYMOND WEISS, M.D.†‡; MERLE K. LOKEN, M.D., Ph.D.* and B. J. KENNEDY, M.D.†

Dedication

Dr. K. W. Stenstrom, "Stennie," gave many of us our first introduction to the use of radionuclides in the practice of medicine as well as guidance in the therapy of lymphomas. Radionuclide studies now offer much help in the management of many disease states. Because the use of ^{67}Gallium relates a radioisotopic imaging procedure to study of the lymphomas, I would like to dedicate this presentation to the memory of my former teacher, K. W. Stenstrom.

^{67}Gallium scans were performed on 26 patients with known malignancies. In 13 patients with a wide variety of primary neoplasms, the presence of tumor was detected in 13 out of 40 known tumor sites. Results were considered poor. The remaining 13 patients had lymphomatous disease and had an over-all detection rate of 17 out of 35 known regions of involvement. Detection was best in extra-abdominal regions. Liver, spleen and retroperitoneal node involvement was poorly detected.

THE DETECTION and localization of soft tissue neoplasms has been demonstrated by the use of ^{67}Gallium.[1] Its use in lymphoma detection particularly has been suggested as an aid in the staging of the extent of the disease process.[2-4] In order to determine its usefulness we studied a group of patients which included a variety of tumor types with metastases as well as a group of lymphomas. In the lymphoma group, new patients undergoing staging procedures as well as patients with recurrent disease were studied.

Methods

The patients in this study were selected from the Oncology Service of the Department of Medicine, a total of 26 patients divided into two groups. The 13 patients in the non-lymphomatous malignancy group represented a wide variety of neoplastic disease (See Tables 1 and 2). The extent of the patients' disease in this group was established by the usual means of investigation and did not necessarily include exploratory laparotomy. Intra-abdominal spread of neoplasm was not evaluated for this study unless biopsy proof or confirmatory findings at autopsy were available. In the lymphoma group of 13 patients, eight patients underwent exploratory laparotomy for staging purposes, another patient with recurrent

TABLE 1
^{67}Gallium Study

Total Number of Patients	26
Non-Lymphomatous Malignancies	13
Lymphomata	13

Clinical distribution of patients.

TABLE 2
Non-Lymphomatous Tumor Types

		Number	^{67}Ga
Adenocarcinoma	Ovary	1	−
Adenocarcinoma	Breast	1	−
Adenocarcinoma	Colon	1	+
Adenocarcinoma	1° Unknown	2	+−
Mixed Embryonal Chorioca. Testis		1	+
Malignant Melanoma		2	++
Transitional Cell (Renal)		1	−
Rhabdomyosarcoma		1	+
Sq. Cell Ca. Lung		1	+
Ewing's Sarcoma		1	+
Chondroblastic Osteosarcoma		1	+
		13	

Distribution of patients by primary tumor type and presence (+) or absence (−) of ^{67}Gallium uptake in any area of known involvement.

*Department of Radiology, Division of Nuclear Medicine, University Hospitals, Minneapolis.
†Department of Medicine, Section of Medical Oncology, University of Minnesota Hospitals, Minneapolis, Minnesota.
‡Presently at: Department of Medicine, University of West Virginia, Morgantown, West Virginia.
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lymphoma underwent surgical exploration of the abdomen. One patient came to autopsy. Laparotomy was not performed in two patients with recurrent lymphoma and in one patient an acute myocardial infarction precluded exploratory staging procedures. In those patients undergoing staging laparotomy, lymphangiography was also performed. The clinical distribution of the lymphoma group is summarized in Table 3.

Each patient to be studied received 3 mCi ^{67}Gallium Citrate.* The material was administered intravenously 48 to 72 hours before scanning. In order to reduce the normal accumulation of gallium in the intestinal tract, each patient received cleansing enemas the evening before and the morning of the scanning procedures.

Imaging was performed with an Anger type gamma camera (Nuclear Chicago Pho Gamma HP or Nuclear Data Radicamera 60). The pulse height analyzer was centered on the 184 kev photo peak of ^{67}Gallium with a 25% window. With a high-energy diverging collimator, multiple views were obtained to include the lymph node regions of the cervical, axillary and inguinal regions as well as the thorax, abdomen and pelvis. Both anterior and posterior views were obtained. In each view 50,000 counts were accumulated.

The number of times that ^{67}Gallium was found to concentrate in a given region was compared to the known occurrence of tumor involvement in that region. The results for each of the lymph node regions (hilar-mediastinal, cervical, supraclavicular, axillary, aortic-iliac and inguinal) were summated. The two patient groups, lymphoma and non-lymphomatous malignancies were studied separately.

*Obtained as sterile, pyrogen-free solution from Diagnostic Isotopes, Inc., Upper Saddle River, N.J. Each vial contained 3 mCi ^{67}Gallium-citrate and 7 mg. of sodium citrate dissolved in 3 ml. of isotonic saline.

Results

The detection of tumor in various areas in the two groups is presented in tabular form, Tables 4 and 5. The results of the non-lymphoma group are listed separately from the lymphoma group.

In the non-lymphoma tumor group, detection rates were quite low (Table 4). Hilar-mediastinal node involvement was detected in only two out of five instances. Lung metastases were found in only one instance out of eight. We were unable to detect liver involvement in five cases. Bone involvement was detected at a somewhat greater rate, six out of nine. In the group of non-lymphomatous neoplasms, detection occurred in a total of 13 out of 40 known tumor bearing regions. Examples are shown in Figures 1 and 2.

The results in the lymphoma group are summarized in Table 5. The extra-abdominal areas of lymph node involvement were most favorable for detection in our series. Hilar-mediastinal involvement was detected in six out of six patients. Abnormal uptake was detected in a total of 17 out of 35 known tumor bearing regions. See Figures

TABLE 3
Clinical Distribution of Lymphoma Group

Stage	Ia	II	IIa	III	IV	Recurrent	Total
Hodgkins	1		1	3	1	3	9
Non-Hodgkins Lymphoma		1				1	2
Reticulum Cell Sarcoma	1					1	2
Total	2	1	1	3	1	5	13

Table 3—Clinical distribution of lymphoma group by stage of disease.

TABLE 4
Summary

Non-Lymphoma Tumor Group 13 Patients

Node Groups:

Hilar Medias.	Cerv.	Supra Clav.	Axill.	Aortic Iliac	Ing.	Lung	Liver	Spleen	GI	Bone
2/5	0/0	0/0	1/2	1/2	2/3	1/8	0/5	0/1	0/5	6/9

Table 4—^{67}Gallium uptake compared to known occurrence of tumor by regions. Non-lymphomatous malignancy group.

TABLE 5
Summary

Lymphoma Group 13 Patients

Node Groups:

Hilar Medias.	Cerv.	Supra Clav.	Axill.	Aortic Iliac	Ing.	Lung	Liver	Spleen	GI	Bone
6/6	0/1	1/3	3/6	2/5	3/4	0/1	0/1	1/5	0/2	1/1

Table 5—^{67}Gallium uptake compared to known occurrence of tumor by regions. Lymphoma Group.

3-5 for typical studies.

Discussion

While the number of abnormal regions studied in each category is somewhat small, we believe there is a trend which may allow for some generalization. The extra-abdominal areas of lymph node involvement were most favorable for detection, particularly in the lymphoma group. Hilar-mediastinal involvement was detected in six out of six patients with lymphoma. Our poorest chances of detection occurred with intra-abdominal disease, notably involvement of the retroperitoneal lymph node chain and the liver and spleen. This is probably due to the normally high accumulation of ^{67}Gallium within the liver, spleen and intestinal tract. Although no abnormally increased areas of concentration in the liver were detected, in two instances "cold" defects were identified and confirmed by colloidal liver scans. Occasionally, surprising results were encountered with marked increased uptake of ^{67}Gallium in regions not otherwise suspected of harboring

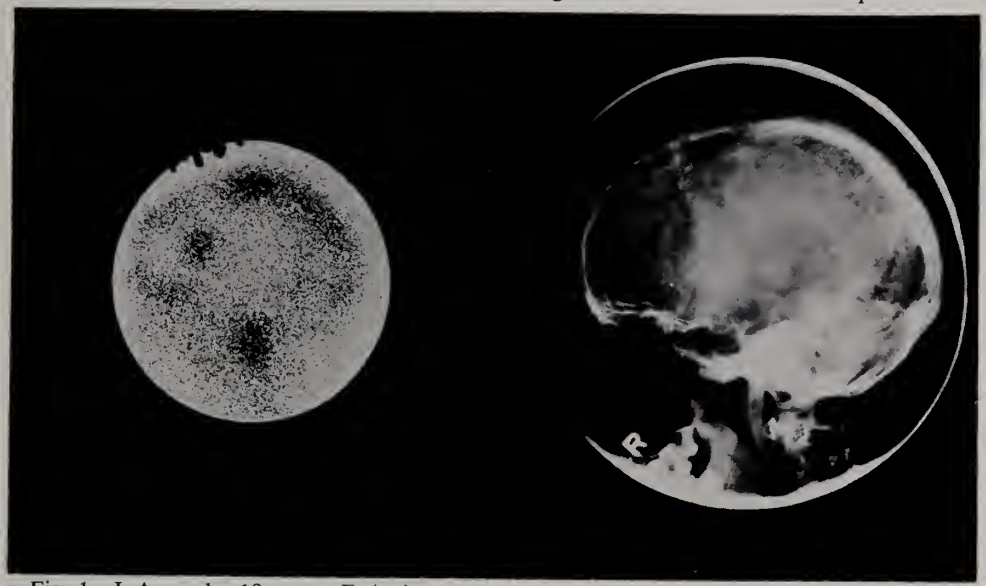


Fig. 1—L.A., male, 18 years. Ewing's sarcoma of sacrum with multiple osseous metastases. (Left) ^{67}Gallium scan of skull region showing multiple abnormal regions of uptake. (Right) Skull Xray; minimal evidence of bone destruction in corresponding regions.

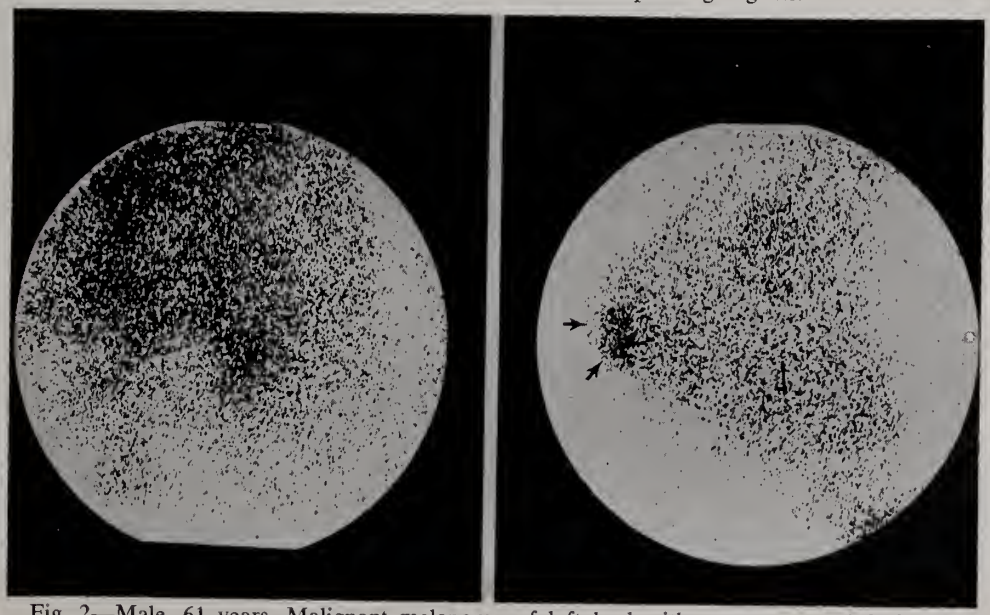


Fig. 2—Male, 61 years. Malignant melanoma of left heel with metastases to left femoral-inguinal region and lung. (Left) ^{67}Gallium scan of left inguinal region demonstrates lymph node involvement. (Right) ^{67}Gallium scan of left heel and ankle region (lateral view) demonstrating ^{67}Gallium in the primary malignant melanoma (arrow).

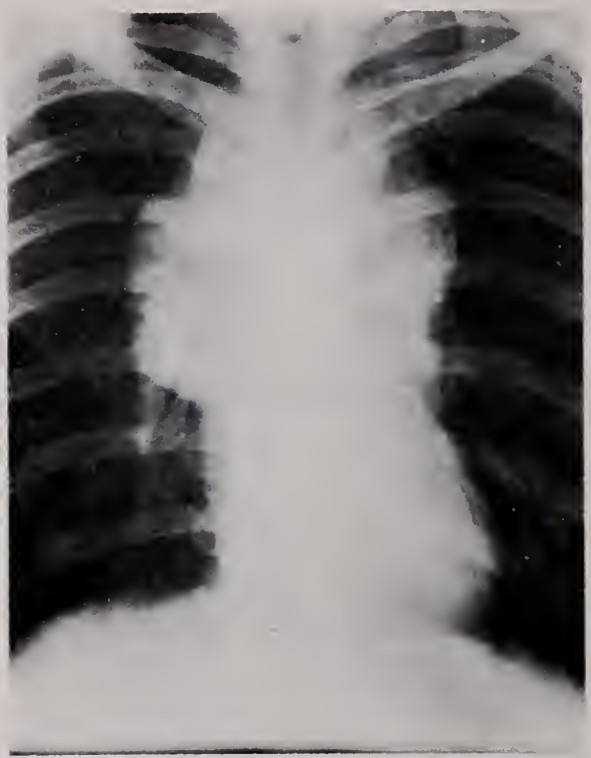




Fig. 3—Male, 23 years. Hodgkin's Disease. Stage IIIb. (A-Left) PA chest Xray. Mediastinal and hilar adenopathy. (B-Right)—Lymphangiogram; abnormal nodes.

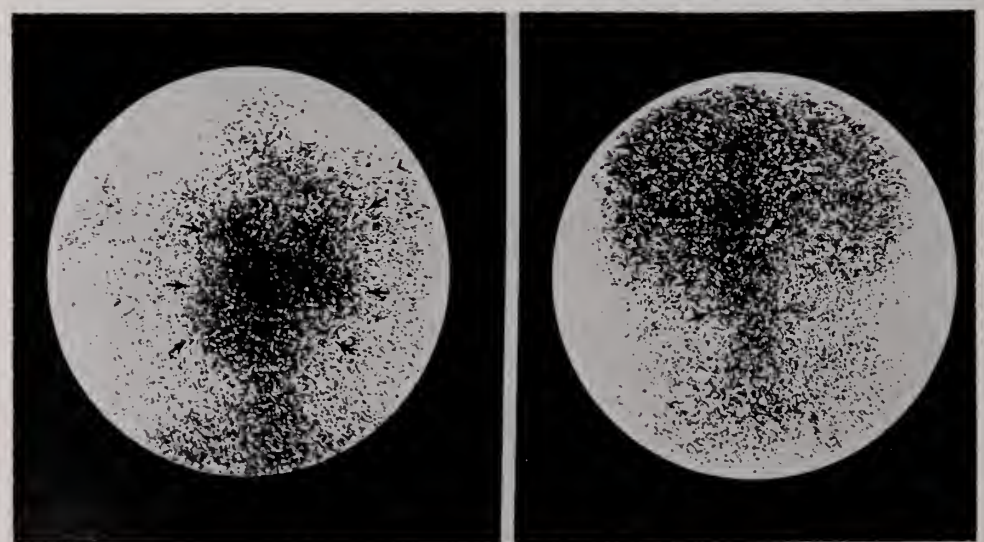


Fig. 3C—(Left) ^{67}Gallium scan of chest region; accumulation in mediastinal and hilar nodes corresponding to Xrays (arrows). (Right) ^{67}Gallium scan of abdomen. Normal accumulation in liver. Abnormal nodal accumulation to right of midline corresponding to lymphangiogram (arrows). Splenic accumulation not demonstrated. Biopsy of liver was normal; spleen specimen showed extensive tumor involvement.

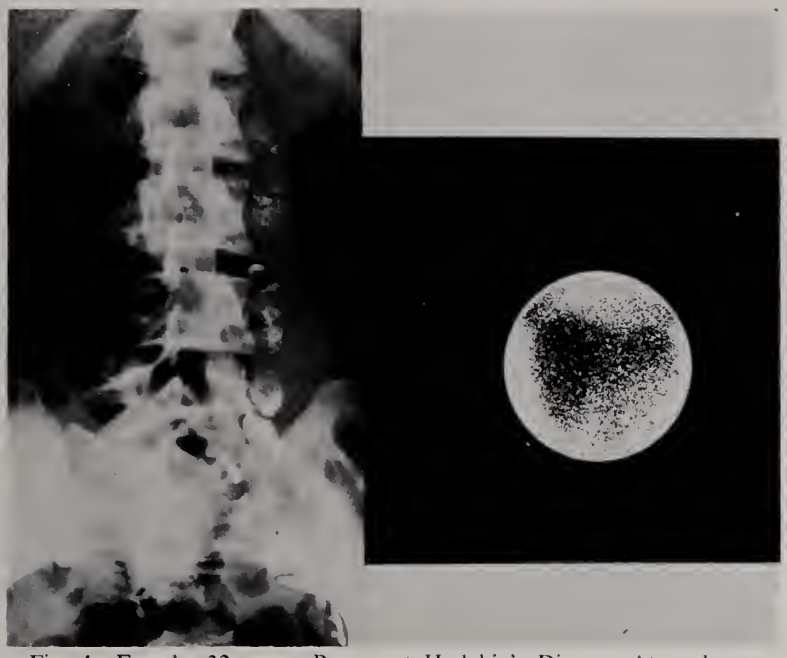


Fig. 4—Female, 32 years. Recurrent Hodgkin's Disease. At exploratory laparotomy found to have involvement of all lymph node group from the diaphragm to the pelvis as well as the spleen. Liver biopsy was normal. (Left) Abnormal abdominal lymphangiogram. (Right) ^{67}Gallium scan of upper abdomen. No abnormal concentration demonstrated.

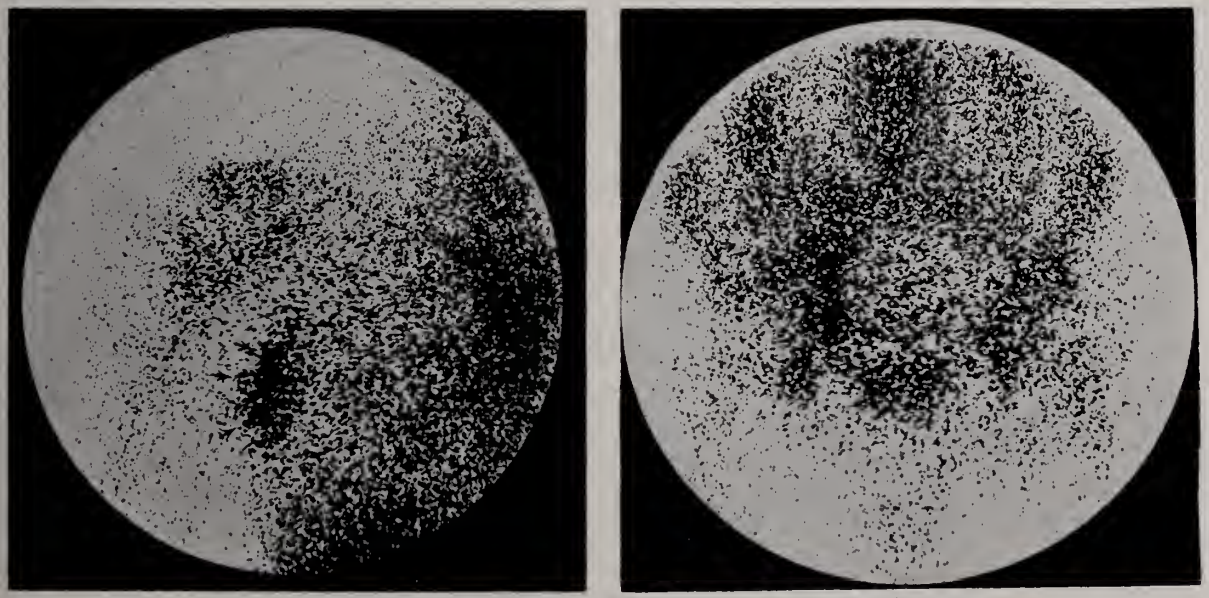


Fig. 5—Male. 26 years. Hodgkin's Disease. Recurrent generalized lymphadenopathy and splenomegaly, due to infectious mononucleosis superimposed upon recurrent Hodgkin's Disease. (Left) ^{67}Gallium scan of right axillary region; abnormal uptake aided choice of biopsy site (arrows). Hodgkin's Disease confirmed by biopsy. (Right) ^{67}Gallium scan of pelvis; abnormal accumulation in right inguinal and iliac lymph node chain.

disease (Figure 1). In a 61-year-old male with primary malignant melanoma of the left heel, there was good correlation of ^{67}Gallium uptake in the primary site and in a large group of inguinal nodes. However, no uptake was demonstrated within a 1.5 cm. metastatic nodule located within his lung (Figure 2). In the non-lymphoma group, results were generally disappointing (Table 5). This is not surprising considering similar reports in the literature.[5,6] While a detection ratio of six out of nine lesions in bone might suggest a possible rationale for this agent, better materials for bone scanning are currently available.

The radioisotopic detection of soft tissue tumors or lymph node involvement is a tool which has been long sought. One need only look at the acceptance of lymphangiography and exploratory laparotomy for staging purposes to appreciate the lengths to which we are willing to go for the discovery and evaluation of the extent of tumor involvement. The role which these procedures have played in developing the modern concept in the treatment of the lymphomas is well known and need not be repeated here. Hopefully, a procedure such as ^{67}Gallium scanning would take its place in the current approach to lymphoma treatment.

^{67}Gallium is moderately expensive, but the economic burden would be considered insignificant if we could answer "yes" to either of two questions:

1. Can ^{67}Gallium scanning replace lymphangiography, which is a slow, tedious procedure and which has a definite morbidity?
2. Can we replace the staging laparotomy?

Unfortunately, at the present time no scanning procedure with ^{67}Gallium or any other agent can replace these clinically accepted procedures. This is not to say that there is no place for ^{67}Gallium scanning; it has shown usefulness in detecting neoplastic involvement in many situations. However, we cannot rely on this procedure alone as a staging examination in the management of lymphomas.

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Dr. Paul Quie

Dr. Paul Quie, professor of pediatrics, laboratory medicine, and pathology at the University of Minnesota, has been named American Legion Memorial Heart Research Professor.

Quie, 49, succeeds Dr. Robert A. Good, president of Sloan Kettering Memorial Cancer Institute in New York, who held the title for 20 years.

A former Markle Scholar, Quie received the E. Mead Johnson Award in 1971 for excellence in pediatric research and a year later received a John Simon Guggenheim Award for a year's study at the Nuffield Department of Clinical Medicine, Radcliffe Infirmary, Oxford, England.

Status of Nuclear Medicine in Minnesota

With Some Notes on Its History

WILLIAM A. WILCOX, M.D.* and JOHN B. MARTA, M.D.†

In the span of little more than 25 years nuclear medicine has evolved from occasional research applications to routine clinical use in the community hospitals throughout the state.

The Radiation Therapy Department at the University of Minnesota under Dr. K. W. Stenstrom was very early involved in the development and use of the first nuclear medicine techniques. Thyroid uptakes, blood volume measurements, and treatment of polycythemia and malignant effusions were among the first procedures adopted in clinical practice during the late 1940's and early 1950's. The first crude attempts at imaging or mapping radioisotope deposition was the counting of certain palpable areas of thyroid or spot counts over a suspected retrosternal thyroid or thyroid metastases.

Moore, at the University of Minnesota, working on the problem of localizing intracranial tumors, first used fluorescein for identifying stained tumor tissue under ultraviolet light in the operating room. He then progressed to diiodofluorescein tagged with ^{131}I, and with the cooperation of Dr. James F. Marvin and Stenstrom, he was able to localize tagged tumors in the intact patient using spot counting with Geiger-Mueller counters and later scintillation counters.[1] This was the beginning of brain scanning.

Within three years of Moore's work localizing tagged tumors with external probes, Cassen et al. of U.C.L.A. described the first rectilinear scanner.[2] Thereafter, during the early 1950's home made versions of the scanner began to be used in the large medical centers of the country. These scanning devices were simply a mechanical adaptation of the existing scintillation detectors, to automatically move the detector in a regular rectilinear pattern across the area of interest, detecting and recording the map of radioactivity deposited there. The early models of the automatic scanner, although slow and troubled by inertia, began to show the potential of nuclear imaging.

The first commercial scanner in Minnesota was a Reed-Curtis model put into service at the University of Minnesota Hospitals in 1957. The following year, St. Joseph's Hospital in St. Paul obtained a Tracer-Lab scanner and this was the first nuclear imaging device to be used in a community hospital in this state. The use of rectilinear scanners rapidly proliferated throughout the state as the models improved and techniques were improved and added and radiopharmaceuticals became available. There are now approximately 56 rectilinear scanners in Minnesota. Although supplanted somewhat in imaging by the scintillation camera, most of these are still in use. Some of those most recently acquired are the dual probe, whole body scanners used almost exclusively for bone scanning. Four of these devices were purchased by institutions in Minnesota during 1972 and 1973. A fifth dual probe scanner has recently been purchased by a community hospital. Five different manufacturers have produced most of these scanners: Picker, Searle-Radiographic (formerly Nuclear-Chicago), General Electric, Ohio-Nuclear, and Abbott.

The scintillation camera or "gamma" camera devised by Hal O. Anger was displayed at national medical meetings in the summer of 1958[3] and became commercially available in 1964. This device uses a single large diameter scintillation detector in various fixed positions to view whole anatomic areas. It thus became possible to ob-

*North Memorial Medical Center, Minneapolis, Minnesota.
†United Hospitals, St. Paul, Minnesota.

serve pictorially, the dynamics of the flow and deposition and clearance of radioactive materials in an organ or system.

The first scintillation camera in the state was installed at the University of Minnesota in 1964. This device rapidly became popular in the medical community. Mt. Sinai and St. Mary's in Minneapolis were the first private hospitals to acquire the gamma camera, and by early 1974, there were 48 of these devices in the state. Four of these have total body imaging capability for use in bone imaging. Two of the four are in community hospitals. Searle Radiographic seems to be the predominant commerical model in use in this state at present, but there are several Picker models and a few Nuclear Data cameras.

Recording media used with both rectilinear scanners and gamma cameras have changed over the years with changing technology and changing clinical emphasis. Mechanical problems on the first rectilinear scanners were greatly alleviated by adapting Teledeltos paper and electrical recording to replace the pen and ink first used. A significant advance for scanners was the photo scan modification portraying the image on x-ray film by a flashing light.[4] This is still the widely preferred medium for scan images despite a number of methods of converting the scan pattern into color on film or paper. The scintillation camera images were originally recorded by means of a modified Polaroid camera. Although still commonly used, this is now supplemented or replaced with 35 mm., 70 mm., or 100 mm. cameras. Highly sophisticated data storage and manipulation modules are being added to the gamma camera systems. The total value of imaging equipment in the state is estimated at close to four million dollars. There are about 40 nuclear medicine departments in the state of Minnesota doing imaging procedures, with 24 of these in the Twin City Metropolitan area.

Paralleling the introduction and continued improvement in the hardware of nuclear medicine has been progress in the available radiopharmaceuticals. Radioisotopes began to be available generally with the development of reactor technology during World War II. In the years since the "Manhattan Project," many additions and changes to the clinical armamentarium have been made and are continuing to be made. Except for thyroid studies, imaging is now mainly done with 99m Technetium compounds obtained from generator systems often utilizing commercial material in kit form tagged in the clinical department as needed with technetium.

An attempt was made to quantitate the amount of nuclear imaging being done in the state of Minnesota and to make some estimate of its importance in hospital practice. Generally speaking, all of the larger hospitals are providing nuclear medicine facilities and many of the small hospitals also have some capabilities. In this survey, it was found most commonly in Minnesota, that the nuclear medicine procedures were divided between two departments of the hospital. Usually, nuclear imaging and other in vivo procedures are done by the Radiology Department and the in vitro or "wet" procedures are the responsibility of the Pathology Department. There are some exceptions. Of the private hospitals in Minneapolis-St. Paul, there are four in which the Nuclear Medicine Department performs all in vivo and most in vitro nuclear medicine procedures. Establishment of the medical specialty of nuclear medicine will probably not have much immediate effect on these arrangements in the community hospitals.

Estimates of the amount of nuclear imaging going on in the state of Minnesota are for the year 1973 and are based on direct contact with

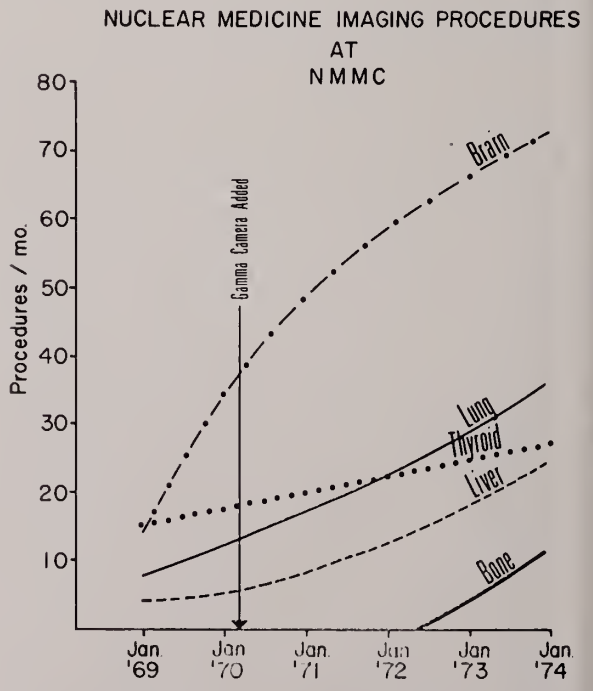


Fig. 1—Growth curves of various nuclear radiology procedures at North Memorial Medical Center over the five-year period ending January 1974.

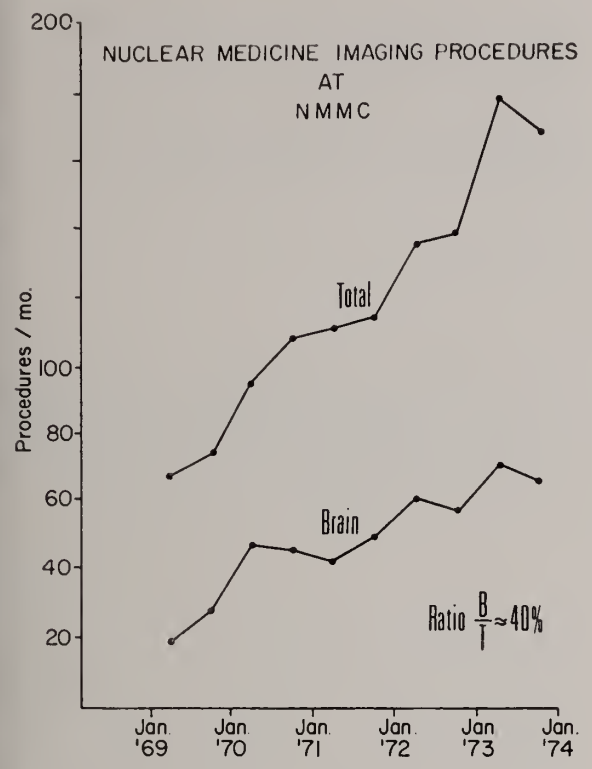


Fig. 2—Five-year history of the nuclear medicine procedures done at North Memorial Medical Center. Procedures per month were averaged at each six-month interval.

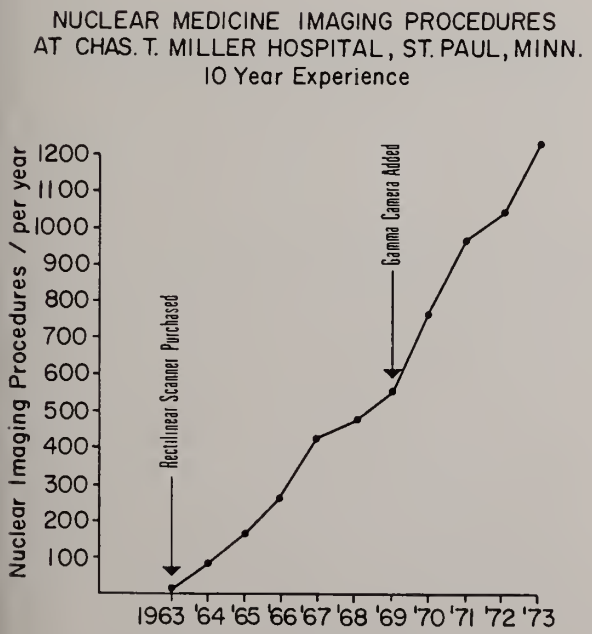


Fig. 3—Ten-year history of nuclear radiology at the Charles T. Miller Hospital in St. Paul.

most of the nuclear medicine facilities throughout the state. The most detailed information is from the institutions with which the authors are directly associated. No attempts was made to count the in vitro procedures performed in the various laboratories. The survey indicates that during 1973, there were about 4,400 nuclear imaging procedures done each month in the state of Minnesota. About 1,800 of these, or 41% were brain imaging procedures. In most of the individual institutions, the brain imaging comprised a surprisingly constant, approximately 40% of the total imaging. This figure is of particular interest at this time in estimating the possible impact on nuclear medicine of the computer-assisted axial tomographic devices (EMI, ACTA scanners).

According to Minnesota Department of Health figures, about 49% of the total acute hospital beds in the state are in the Twin City Metropolitan area where about 49% of the total 1973 hospital admissions occurred. In the same year, our figures show that about 75% of the state's total nuclear imaging procedures were done in Minneapolis-St. Paul area hospitals. Apparently, nuclear imaging is much more frequently used in the larger metropolitan hospitals of this state.

All of the institutions contacted report steady increase in nuclear imaging over the past several years. The growth of nuclear imaging of various organs plotted against time over the past five years is shown in Figure 1 for North Memorial Medical Center. This is probably a fairly typical experience for a large community hospital. Particularly notable, is the rapidly increasing utilization of bone imaging since the release of the new phosphate substances in kit form for general use. In Figure 2, total imaging and brain imaging procedures at North Memorial Medical Center are plotted versus time. Here again steady growth in usage is evident. During 1973, approximately 6½% of patients admitted to this hospital received some type of nuclear imaging procedure. The ten-year history of nuclear imaging at Charles T. Miller Hospital in St. Paul is shown in Figure 3.

Based on present data it appears that imaging by the techniques of nuclear medicine has become an accepted part of clinical practice and will be used with increasing frequency. One might speculate on what progress can be expected: (1) There probably will be further improvement in image quality based on instrument improvement. (2) New techniques based on new radiopharmaceuti-

cals can be expected. (3) More useful dynamic function and vascular information will be available as the potential of computers to manipulate data is more fully utilized. An inhibiting factor now appearing which clinical nuclear medicine must consider is the growing concern by various groups for possible hazards of air transport of radiopharmaceuticals. If air transport is restricted to any serious degree, it will be considerably more difficult, perhaps impossible, to provide nuclear medicine services to patients as needed.

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Cover Photo

"Feeding the Jay"

The cover photograph of a blue jay feasting on a cob of corn was taken on a cold morning in January, 1974, through the family room window of Dr. Hugh J. Williams' home in North Oaks. On such a day there is a constant visitation to the feeder by a variety of hardy, hungry birds. This photo was taken on Kodacolor II film through a 270 mm telephoto lens.

Dr. Williams is radiologist at the St. Paul Children's Hospital and has enjoyed the hobby of wild bird photography for several years. He has an outstanding collection of bird photographs taken by him and has on occasions exhibited them for everyone's enjoyment.

Dr. Oscar Lipschultz, radiologist at Hennepin County General Hospital, encouraged Dr. Williams to submit the cover photograph to the editors of MINNESOTA MEDICINE.

Benefit vs Risk in the Practice of Nuclear Medicine*

MERLE K. LOKEN, M.D., Ph.D.† and J. THOMAS PAYNE, Ph.D.‡

Quantitative determinations of benefit vs. risk in using radiations in medical practice have been made for lung scanning and for ophalopelvimetry. Despite careful consideration of all available data, these determinations are, at best good estimates. Thus, good clinical judgment remains paramount in the practice of radiation medicine—to provide the greatest patient benefit to risk ratio.

During his 30 years at the University of Minnesota Dr. K. W. Stenstrom made many significant contributions to the practice of Radiation Medicine, one of these was the introduction of radioisotopes for diagnostic and therapeutic purposes, thus laying the foundation for Nuclear Medicine. A 4MeV Vandegraff generator installed in the Physics Department in 1940 provided radioactive sodium and chlorine to be used as tracers for biomedical investigation. Following World War II when reactor produced radioisotopes were made available, the groundwork had been laid for clinical application of radioisotopes of Iodine for evaluation of thyroid gland activity and treatment of hyperthyroidism, and radioactive Phosphorus for treatment of patients with polycythemia vera.

Because of this contribution to Nuclear Medicine together with his constant concern for radiation safety, it is fitting that an article on benefits and risks to patients undergoing procedures in our Nuclear Medicine Clinic be included in this special issue of Minnesota Medicine dedicated to the memory of our mentor, colleague and friend, Karl Wilhelm Stenstrom.

The phenomenal growth that Nuclear Medicine has experienced during the past two decades can be attributed primarily to the tracer concept. By appropriate choice of a radioactive label, measurements of radioactivity may be made outside the body using appropriate radiation detectors. Thus, metabolic, functional and structural abnormalities that prior to the advent of radioisotope tracer methodology could only be described in terms of the total patient, are now localized to particular organs or to regions within these organs.

The various procedures which constitute the practice of Nuclear Medicine at our institution were considered in an earlier publication in this journal.[1] These procedures were divided into five categories, the first of which related to various in vitro or laboratory techniques. The next three summarized our studies of organ visualization, function and blood flow. Further consideration will be given here to these applications of radioisotopes in the practice of medicine, as they are responsible for almost all of the radiation exposure of patients from diagnostic nuclear medical procedures and for the majority of the radiation to personnel working in this field.

The final category of Nuclear Medicine relates to therapeutic uses of radioisotopes. Contrary to the belief of some, therapy with radioisotopes comprises but a small portion (less than 5%) of Nuclear Medicine despite the fact that during the first 50 years after the discovery of radioactivity, therapy alone was practiced. As man-made radionuclides became available, there was great hope that these materials would prove effective as therapeutic agents and thus aid in the eradication of cancer. Unfortunately, this desired result has turned out to be the exception rather than the rule; in only limited instances have radioisotopes served effectively as therapeutic tools. In these few instances, the radioactivity can

*From the Division of Nuclear Medicine, Department of Radiology, University of Minnesota Hospitals.
†Professor and Director, Division of Nuclear Medicine.
‡Assistant Professor.

be selectively localized for a protracted period in the tissue to be irradiated. Only in this way is it possible to obtain a satisfactory therapeutic ratio, i.e. satisfactory ratio of radiation to selected tissues (cancer, etc.) to that delivered to normal surrounding tissues.

Instrumentation of Nuclear Medicine

A wide variety of instruments are available for use in these studies, all of which have some means of detecting and recording radioactivity. Almost all of these instruments employ a scintillation crystal detector coupled with a spectrometer for analysis of gamma-ray energies of the radionuclide being used. Beyond the step of detection, instruments differ depending upon their particular application. Those used for assay of radioactivity generally employ a scaler for totalling the observed disintegration events. If information is desired on the rate of uptake and clearance of a radioisotope from an organ, (such as in studying the function of a kidney) a rate meter and strip chart recorder are usually employed. Images (scintiphotograms) of the distribution of radioactivity in body organs are obtained using a moving detector (rectilinear scanner) or by the use of a large crystal detector as a stationary imaging device (scintillation camera). The camera is the more versatile of the instruments and is used for studies in which dynamic function data are desired in addition to scintiphotograms. There appears to be little doubt that future developments in camera-like systems will provide significant improvements in resolution in scintiphotograms so that image quality will approach that currently available in conventional radiographic procedures.

With the aid of computer analysis, currently an integral part of many of the diagnostic procedures in Nuclear Medicine practice, quantitative information on regional function and blood flow can be obtained for most body organs.

Choice of Radiopharmaceuticals

The performance of the various procedures which comprise Nuclear Medicine, particularly those carried out *in vivo*, requires special consideration of radionuclides as summarized in Table 1. As this Table implies, the ideal radiopharmaceutical may be characterized as one that is readily available at reasonable cost and provides maximum diagnostic information (or the most optimal radiation therapy) at the least potential danger (toxicity and radiation dose) and discomfort to the patient. The maximum diagnostic information or most optimal therapy of a radiopharmaceutical will depend upon tissue specificity and distribution within the tissue. There are a variety of mechanisms by which these agents might localize as are listed in Table 2.[2]

In general, after intravenous administration of a radiopharmaceutical, this activity in the blood decreases steadily while the activity of the target organ increases. The radioactivity may be retained within the target organ for varying periods of time, depending upon the mechanisms of localization. For example, the time may be relatively short in cases of active transport or diffusion, whereas

TABLE 1
Consideration of the Choice of Radiopharmaceuticals

1. Tissue specificity
2. Tissue distribution
3. Availability
4. Cost
5. Toxicity
6. Effective half life
   - a. Physical
   - b. Biological
7. Character and energy of radioactive emissions
8. Radiation dose

TABLE 2
Mechanisms of Localization

1. Active transport
   - a. Thyroid scanning with iodide or pertechnetate
   - b. Liver scanning with Rose Bengal or Cholegrafin
   - c. Renal scanning with Chlormerodrin, Hippuric acid or labeled Chelate
   - d. Pancreas or parathyroid scanning with selenomethionine
   - e. Salivary gland scanning with pertechnetate
2. Phagocytosis
   - a. Liver scanning with colloidal material
   - b. Spleen scanning with colloidal material
   - c. Bone marrow scanning with colloidal material
3. Compartmental localization
   - a. Cardiac scanning for pericardial effusion
   - b. Mediastinal scanning for aneurysms
   - c. Placental scanning for placenta previa
   - d. Studies of organ blood flow
   - e. Transit of cerebrospinal fluid
   - f. Cerebral aneurysms and A-V malformation
4. Cell sequestration
   - a. Spleen scanning with damaged red cells (heat or chemical)
5. Capillary blockade
   - a. Lung scanning with particles (approximately 50 micron diameter)
   - b. Renal scanning with particles
   - c. Brain scanning with particles
   - d. Cardiac shunt evaluation with particles
6. Simple or exchange diffusion
   - a. Bone scanning
   - b. Brain scanning
   - c. Thyroid scanning with pertechnetate
   - d. Pancreas scanning with selenomethionine
   - e. Measurements of blood flow with Xenon

retention tends to be somewhat longer in localization by capillary blockade, phagocytosis, or with an agent that is retained within the blood stream (compartmental localization). These various mechanisms by which radioisotopes pass through organs serve as the basis for the various procedures of organ visualization, measurements of organ function, and blood flow as previously discussed. A list of some of the radionuclides more commonly used in the practice of Nuclear Medicine today is shown in Table 3. These radionuclides are grouped according to physical half life. This together with information on biological clearance times (biological half life), the amount administered, the distribution in the body and equilibrium dose rate constant (gram rads per μCi

TABLE 3
Gamma Emitters Used in Nuclear Medicine

Group	Isotope	Half Life	Disintegration Scheme	Principle Energy	Rad/uCi hr. (for 2Kg. sphere)
I.	15_{O}	2.1 min	β +	0.511 Mev	1.89
< 1 hr.	13_{N}	10 min	β +	0.511	1.35
	11_{C}	20.4 min	β +	0.511	1.15
II.	$113m_{In}$	1.7	I.T.	0.393	0.37
1-10 hr.	18_{F}	1.9	β +	0.511	0.88
	132_{I}	2.3	β −	0.67	1.55
	$87m_{Sr}$	2.8	I.T.	0.380	0.22
	$99m_{Tc}$	6	I.T.	0.140	0.07
	52_{Fe}	8	β +	0.511	0.63
III.	42_{K}	12.5	β −	1.50	2.83
10-24 hr.	64_{Cu}	12.8	EC, β −, β +	0.511	—
	123_{I}	13	EC	0.159	0.11
	24_{Na}	15	β −	1.37, 2.7	2.36
IV.	129_{Cs}	1.3 da	EC	0.375	—
1-7 days	82_{Br}	1.5	β −	0.554	—
				0.619	—
	197_{Hg}	2.7	EC	0.77	0.21
	198_{Au}	2.7	β −	0.411	0.85
	99_{Mo}	2.8	β −	0.141	0.86
	111_{In}	2.8	EC	0.173	0.31
				0.247	—
	67_{Ga}	3.2	EC	0.093	0.08
				0.296	—
	47_{Ca}	4.7	β −	1.3	—
	133_{Xe}	5.3	β −	0.081	0.31
V.	131_{I}	8.1	β −	0.36	0.56
1 week to	131_{Cs}	9.6	EC	0.028	—
1 month	32_{P}	14.3	β −	1.710	1.48
	74_{As}	18.0	EC, β +, β −	0.511	—
				0.596	—
	86_{Rb}	18.7	β −	1.08	—
	51_{Cr}	28.0	EC	0.32	0.02
VI.	84_{Rb}	33 days	EC, β +	0.511	0.45
greater				0.88	—
than 1	127_{Xe}	36.4	EC	0.203	—
month	59_{Fe}	45.1	β −	1.09	0.65
				1.29	—
	203_{Hg}	46.9	β −	0.279	0.30
	125_{I}	60.0	EC	0.028	0.09
				0.035	—
	85_{Sr}	64	EC	0.514	0.10
				0.811	—
	75_{Se}	121.8	EC	0.136	0.15
				0.265	—
	57_{Co}	270	EC	0.122	0.06
	22_{Na}	2.6 yr.	β +	0.511	1.00
	60_{Co}	5.2	β −	1.17	1.07
				1.33	—
	85_{Kr}	10.3	β −	0.514	—

hr)* will permit radiation doses to be determined. The biological half life of radionuclides will vary, depending upon the pharmaceutical form in which they are administered. As an example of the radiation dose to an organ using different radiopharmaceuticals, consider a liver study using 131-Iodine albumin colloid, 131-Iodine Rose Bengal or 99m-Technetium Sulfur colloid. The following calculations of radiation dose to the liver were made using the absorbed fraction dosimetry system as outlined in the Medical Internal Radiation Dose (MIRD) pamphlets.

a. 131-Iodine Albumin Colloid
Liver mass = 1850 gm
Radioactivity administered = 300 microcuries
Effective clearance half time = one day = 24 hr
Cumulative calculated concentration

$$= 5.6 \frac{\text{uci hr}}{\text{gm}}$$

$$\text{Energy absorbed } \sum \Delta_i \phi_i = .5373 \quad \frac{\text{gm rads}}{\text{uci hr}}$$

$$\text{Liver Dose} = \left(5.6 \frac{\text{uci hr}}{\text{gm}}\right) \cdot \left(.5373 \frac{\text{gr rads}}{\text{uci hr}}\right)$$

Liver Dose = 3.01 rad

*Rad/μCi hr for a two kilogram sphere are included in Table 3 for those radionuclides for which appropriate data were available from MIRD pamphlets.[3]

b. 131-Iodine Rose Bengal
Liver mass = 1850 gm
Radioactivity administered = 300 microcuries
Effective clearance half time = 1 hr
Cumulative calculated concentration

$$= .23 \frac{\text{uci hr}}{\text{gm}}$$

$$\text{Energy absorbed } \sum \Delta_i \phi_i = .5373$$

$$\text{Liver Dose} = \left(0.23 \frac{\text{uci hr}}{\text{gm}}\right) \cdot \left(.5373 \frac{\text{gm rad}}{\text{uci hr}}\right)$$

Liver Dose = 0.125 rad

c. 99m-Technetium Sulfur Colloid
Liver mass = 1850 gm
Radioactivity administered = 3000 microcuries (3 millicuries)
Effective clearance (half time) = Physical decay 6 hr
Cumulative calculated concentration

$$= 14 \frac{\text{uci hr}}{\text{gm}}$$

$$\text{Energy absorbed } \sum \Delta_i \phi_i = .5373 \quad \frac{\text{gr rad}}{\text{uci hr}}$$

$$\text{Liver Dose} = \left(14 \frac{\text{uci hr}}{\text{gm}}\right) \quad \left(.043 \frac{\text{gr rad}}{\text{uci hr}}\right)$$

Liver Dose = 1.1 rad

It is apparent that the effective clearance can greatly affect the radiation dose as indicated by the rather large dose from 131 I-Albumin colloid

TABLE 4
Procedures in Nuclear Medicine Performed with ^{99m}Technetium

Pertechnetate
1. Brain
2. Thyroid
3. Salivary Glands
4. GI tract
5. Blood flow
   a. Cerebral
   b. Cardiac
   c. Pulmonary
6. Blood pool
   a. Placenta
   b. Pericardium
   c. Mediastinum
   d. Aneurysms

Albumin
1. Subarachnoid space
2. Blood volume
3. Blood flow (see above)
4. Blood pool (see above)

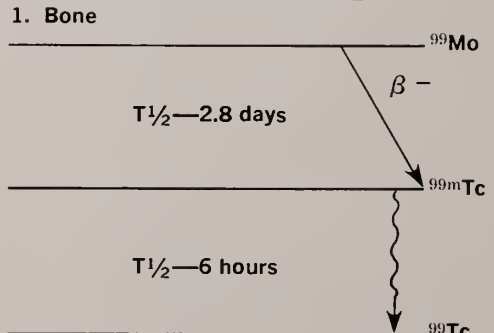
Erythrocytes
1. Blood volume
2. Spleen

DTPA
1. Kidney (GFR)
2. Placenta

Albumin Particles (aggregates or spheres)
1. Blood flow
   a. Lung
   b. Extremities
   c. Coronary
   d. Renal
   e. Cardiac shunts

Sulfur Colloid
1. Liver
2. Spleen
3. Bone marrow

Polyphosphate or Diphosphonate
1. Bone



as compared to 133 I-Rose Bengal. Likewise the energy absorbed is important as shown by comparing the 99m Tc—S colloid with the 131 I-Albumin colloid. Because of its unique properties, 99m-Technetium is one of the radionuclides receiving much attention in the practice of Nuclear Medicine. This nuclide has nearly ideal physical characteristics (six hour physical half life, single gamma energy of 140 kev and no beta emissions). A variety of pharmaceuticals labeled with 99m Tc have been formulated for various procedures as summarized in Table 4. Radiation doses delivered to critical organs in the body by compounds selected from this group will be shown in Tables that follow.

Another radionuclide with multiple uses is 133-Xenon. It may be administered either as a gas or dissolved in sterile saline and administered intravenously or by catheter into the arterial supply of body organs for assessment of blood flow. Table 5 summarizes various uses made of 133-Xenon in the practice of Nuclear Medicine at the University of Minnesota Hospitals. Radiation doses to body organs from 133-Xenon will be shown in tables to follow.

Radiation of Man in the Practice of Nuclear Medicine

Any discussion of radiation exposure or radiation dose requires a brief consideration of units of measurement. During the first few years after the discovery of ionizing radiations, the only method of radiation measurement generally used was the erythema dose (reddening of the exposed skin). It was soon recognized that this unit was dependent on both the quality (energy) of the radiation and the biological variability of different individuals' skin. In 1928 at the Second International Congress of Radiology, the Roentgen as a unit of radiation quantity based on ionization of air, was defined. This unit although reasonably reliable is restricted by definition to the radiation of air. Thus a quantitative measure of radiant energy absorbed was sought and in 1956 the 'rad' was defined as a unit of absorbed dose; one rad being equal to 100 ergs of energy absorbed in one gram of any material.* Finally, since different types of radiations (alphas, betas, neutrons, Xrays, etc.) produce greater or lesser amounts of biological change for the same rad dose, another unit, the 'rem' (radiation equivalent mammal) was introduced to account for these different biological responses. By definition: 1 rem = 1 rad x RBE, where the RBE is the relative biological effectiveness value for the type of radiation and biological response in question. The RBE of 250 kVp Xrays with a one millimeter of copper half value layer is defined to be unity. Typical RBE values for other radiations are:

Gamma rays, beta particles — 1
neutrons — 5-10
alpha particles — 10-20

Since the RBE for Xrays, gamma rays and beta

*In the radiation of air, 1 roentgen = 0.87 rad.

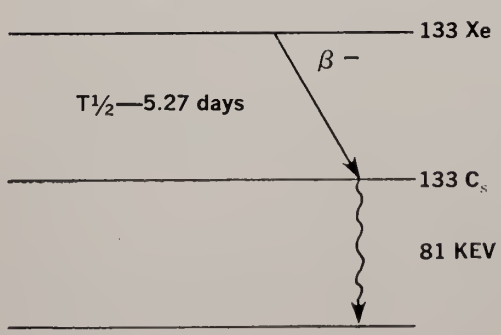
TABLE 5
Procedures in Nuclear Medicine Performed with ^{133}Xenon

Inhalation
1. Ventilation
2. Blood flow
   a. Cerebral
3. Cardiac dynamics

Intravenous Injection
1. Pulmonary blood flow
2. Cardiac dynamics
3. Ventilation

Intramuscular Injection
1. Muscle blood flow

Intra-arterial Injection
1. Blood flow
   a. Cerebral
   b. Coronary
   c. Renal
   d. Hepatic
   e. Extremities



particles is near unity, the rem dose and the rad dose are essentially equal in magnitude for these radiations.

"What do we know about the effects of radiation to man?" To answer this, we must recognize that man has been living in a "sea" of radiation since his inception. Each year in Minnesota we receive approximately 150 millirads from background radiation (cosmic radiation and terrestial radioactive materials). At high altitudes there is considerably more cosmic radiation and inhabitants in these areas may receive 500 millirads per year. Some regions of the earth's crust contain a high radioactive content and individuals in this environment may receive as much as 1800 millirads annually. Over the three quarters of a century since the discovery of Xrays by Roentgen (1895) and of radioactivity by Becquerel (1896) the total amount of radiation received by man has gradually increased steadily due primarily to the addition of medical usage. Early indiscriminant use of these radiations showed them to be hazardous as well as beneficial. Many early users received severe skin burns most often on the fingers, causing ulcerations which in some cases progressed to necrosis of soft tissue and bone requiring grafting and/or amputation. The lethality of high doses of radiation and its carcinogenic property were established soon thereafter. As time progressed evidence mounted indicating that radiation produced genetic as well as somatic damage. The effects of radiation on man have been substantiated from studies of atomic bomb victims (Hiroshima and Nagasaki, nuclear accidents, radiotherapy patients, and continued follow-up of the early radiation workers.

Knowing that radiation can cause damage raises three questions:

1. What is the radiation dose effect for various organs and whole body?
2. Will this relationship be dependent on the dose rate?
3. Is there a threshold dose for all or some effects below which dose no effect is observed?

In the light of information available these questions will be discussed, considering first somatic and then genetic effects.

Somatic Effects of Radiation

The induction of cancer by low doses of radiation can only be inferred in terms of an excess in cancer cases above the natural incidence. Due to the relatively low incidence of cancer, the time lapse between irradiation and cancer appearance, large numbers of people must be studied over many years to arrive at statistically significant results. This task has been difficult and to date has not provided all the information necessary to establish a dose-effect relationship at low dose levels (less than 100 rem). Some information on the relationship between radiation dose and leukemia has been obtained from atomic bomb victims and in some cases from radiation therapy patients such as those receiving x-ray treatments for ankylosing spondylitis.[4] Survivors of the bomb blasts at Hiroshima and Nagasaki (82,000 cases) with radiation exposures up to 100 rem have shown the same leukemia incidence as the unexposed population in Japan.[4] For radiation doses above 100 rem, the number of deaths added to normal leukemia deaths a year were determined to be 250 per 100 rems per million of the population so irradiated. To estimate the risk at low doses it is necessary to extrapolate this 'apparent' linear relationship through the origin at zero dose, thus assuming a non-threshold response. From this fitted straight-line it can be estimated that the risk of leukemia is one or two cases per rem per year for one million persons irradiated.[5]

It is important to emphasize that no data exist to substantiate that the above risk is indeed real. Thus the assumption of a linear response, hence no threshold, is conservative and would appear, if anything, to overestimate the likelihood of radiation leukemogenesis. From experimental evidence in radiobiology, as well as from clinical experience in radiotherapy, fractionated delivery of a radiation dose, i.e., low dose rates, can be tolerated to a greater extent than the delivery of a single dose of the same magnitude. This indicates an element of recovery from radiation at low dose rates and thus, one cannot simply add fractionated small doses to predict a given effect. However, due to a lack of definitive data on radiation effects at low dose and low dose rates, a linear non-threshold hypothesis is generally assumed for the calculations of leukemia incidence from radiation. This assumption is likewise used in assessing the risk of other cancers from radiation. This risk has been estimated to be from 0.1 to 2 cases per million population per year per rem depending upon the cancer site.[5] The 1973 estimate of the

American Cancer Society for the number of cancer deaths per million population per year is given in Table 6. Conservative estimates of the additional risk from one rem of radiation delivered to a population of 1 million show this to be considerably less than 1 percent.[5] Again, no data exist to substantiate that this risk is indeed real.

TABLE 6

Cancer	Number of deaths per year per million population[21]
Leukemia	72
Lung	350
Breast	165
GI tract	300
Other	200

In the nine year follow-up of 30 adolescents and children receiving a cumulative dose between 2 and 32 mCi of ^{131}I for treatment of thyrotoxicosis, no deaths or evidence of cancer or leukemia were seen.[6] In a cooperative study of therapy for thyrotoxicosis involving 36,000 patients,[7] 22,000 were treated with ^{131}I and the remaining 14,000 with antithyroid drugs and/or surgery. The incidence of leukemia in the two groups was not statistically different.

Effects other than cancer may be produced by radiation. The irradiation of the fetus in utero may lead to such somatic effects as impairment of growth, microcephaly and mental retardation. From reports by Zappert[8] and Goldstein and Murphy,[9] microcephaly with concomitant mental retardation and general growth impairment were found in the offspring of mothers treated with radium and x-rays for tumors of the uterus, and/or abnormal uterine bleeding during pregnancy. In most instances the total fetal radiation doses exceeded 250 rads. From the data accumulated from victims of the atomic bomb blasts, 'profound' mental retardation was not observed in children who received less than 50 rads in utero ('profound' retardation was applied to those children who were unable to perform simple calculations, to make simple conversation, to care for themselves, or were completely unmanageable). Other dose-effect data likewise fail to substantiate any increase in abnormalities of growth and development following exposures of the fetus to low doses of less than 50 rem.

Genetic Effects of Radiation

Although Müller reported in 1927 that radiation causes genetic mutations, it was not until after World War II that genetic risks were regarded as a significant factor in determining maximum permissible radiation doses (MPD) to the general population. In 1956, the National Academy of Sciences adopted the concept that the total accumulated gonadal dose be limited to 10 roentgens up to 30 years of age. This age was chosen as representing the mean age for reproduction. This dose level was subsequently included in the 1957 recommendations of the National Committee of Radiation Protection (NCRP). At that time it was estimated that about half the radiation of man was derived from medical sources and the 10 roentgen limit included this exposure. Subsequently the Federal Radiation Council removed medical radiation from the MPD and took five roentgens as the 30 year limit for genetic dose. Thus the 170 milliroentgens per year was established as an annual genetic MPD. On the other hand there is no stated limitation on radiation exposure to the general population from medical sources.[5]

Genetic damage results from a chance alteration (deletion or addition) of one or more nucleotides in DNA, or a break in the nucleoprotein structure of the chromosome. The addition or deletion of nucleotide from DNA will shift the coding sequence and thus alter the amino acid arrangement in protein synthesis. Chromosome breaks or aberrations will generally result in the loss of genetic information which may have severe consequences.

The general principles used in assessing genetic risk can be stated as follows: "Mutations, spontaneous or induced, are considered to be harmful so that anything that causes an increase in the mutation rate should be avoided if possible." From data accumulated from studies in which genetic material received high doses of radiation, it was found that the number of mutations produced was proportional to the dose delivered. No human data are available on genetic effects from small doses so that, as with somatic effects at low doses, a linear extrapolation from high dose data is used to estimate low dose effects. The radiation dose-effect relationship as determined by laboratory animal studies appears to support a linear non-threshold relationship. The effect is generally assumed to be dose rate independent although recent studies show this to be an incorrect assumption, at least in studies using laboratory mice.[5] In a recent report, the Committee on Biological Effects of Ionizing Radiation (BEIR)

has estimated the genetic doubling dose (that dose necessary to double the spontaneous mutation rate) to lie between 20 and 200 rads.

Genetic effects are usually much more difficult to detect in humans than are somatic effects. Genetic effects do, however, have far reaching implications extending from one generation to another and thus for long term considerations (over many generations), genetic effects become more important in radiation hazard considerations than somatic effects.

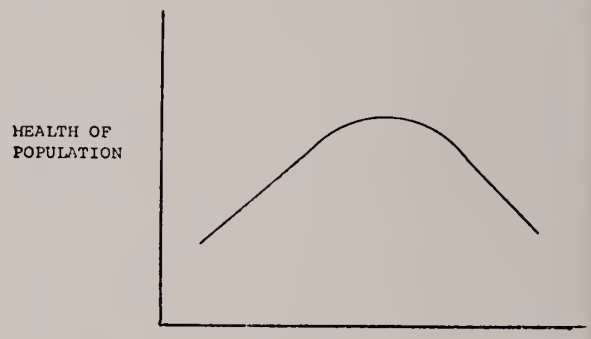
Dominant mutations disappear quite rapidly from a population whereas recessive mutations (as many radiation induced mutations are considered to be) add to the existing pool of potentially harmful mutations and therefore may persist through many generations. However, it may not be appropriate to consider all genetic doses as cumulative since in mice a reduced effect has been observed with protracted radiation because of repair and recovery. After examining offsprings from 71,280 Japanese pregnancies (1948-1953) the Atomic Bomb Casualty Commission found no apparent genetic radiation damage as might be manifested by malformations, stillbirths or neonatal deaths.[10]

The assessment of the genetic risk as stated by the BEIR Committee can be most confidently made for the human population when viewed as the risk relative to the natural background. If the genetic radiation dose is well below background radiation, it is reasonable to assume that any genetic effects attributable to man made radiations will be less in quantity and no different in nature from those associated with background radiation. Taylor has summarized very succinctly, the present understanding on the effects of radiation to humans.[4] "Our knowledge of dose-effect in the region below 1 rad or 1 rem can be summed up very easily. Despite many millions of dollars worth of experimental studies carried out the world over, and despite many attempts at the clinical level, no one has yet been able to establish a dose-effect relationship in this range."

The Benefit—Risk Ratio in Nuclear Medicine

From the foregoing discussion of effects of radiation on biological systems, it must be assumed that any exposure to radiation carries some risk for the development of somatic damage, including leukemia and other malignancies, and of genetic damage. This implies that down to the lowest levels of radiation dose, the risk of inducing disease or disability is dose dependent, i.e., that there is no threshold and hence no wholly safe dose of radiation.

Thus the physician involved in the practice of Nuclear Medicine must be convinced that each and every procedure provides sufficiently useful clinical information to warrant the radiation exposure to patients; and, that this information is obtained at the least risk (lowest possible radiation exposure) to the patient. By providing useful



Figure

TABLE 7
Comparison of Lung Scanning Agents*

Date Introduced	1963	1966	1969
Agent	^{131}I-MAA	^{113m}In-Fe(OH)$_3$	^{99m}Tc-Fe(OH)$_2$
Principle gamma (kev)	364	393	140
Nonpenetrating radiation (g-rads/uCi hr)	0.42	0.29	0.04
T½ physical	8.1d	1.7h	6.0h
T½ biologic	9.0h	16.0h	22.0h
mCi injected	0.35	2.0	3.5
Lung dose (mrad)	1,500	1,060	875
Total body dose (mrad)	700	50	50
Examinations per year per thousand inpatient beds	450	750	900

*Data from Johns Hopkins Hospital.[8]

clinical information, the practice of Nuclear Medicine should improve the overall average health of the general population. If this improvement in health is greater than the health hazards the overall health of the population should improve for 'reasonable' radiation exposures as shown in the Figure. Hopefully in all instances, the Nuclear Medicine physician is practicing on the positive slope of this curve, near its apex.

By improving radiopharmaceuticals and instrumentation in Nuclear Medicine, it has been possible to increase the information content, hence diagnostic accuracy, of Nuclear Medicine procedures while at the same time decreasing radiation exposure. An example of how this has been accomplished in the scanning of the lung at John Hopkins Hospital is shown in Table 7.[10] This trend of decreasing radiation exposure for procedure has been observed in numerous instances in the practice of Nuclear Medicine during the past decade. It is reasonable to expect that the trend will continue and that additional short-lived radiopharmaceuticals will be introduced to permit further reductions to be made in radiation exposure.

Just as difficulties arise in assessing risk, so it is difficult to establish the benefit or procedures performed in the practice of Nuclear Medicine. However, quantitative judgments can be made on benefits versus risks by careful attention to details. This point is illustrated by a South African study of the complications of pregnancy associated with pelvis dimensions.[10] These investigators used a double blind approach to ascertain the benefit of cephalopelvimetry in pregnant women who had previously had problems in delivery. Earlier studies which suggested a possible radiation hazard from this procedure indicated a need to determine the possible benefit that might be derived from the necessary radiation exposure. With 300 patients referred to Radiology for pelvimetry, the examination was either performed or not performed on the basis of random allocation. When pelvimetry was not performed, perinatal mortality was 5%, whereas with pelvimetry, the rate was 3%. It was also found that the incidences of neonatal asphyxia were 20% in patients with no radiographic studies and 13% in patients with x-ray pelvimetry. Although the numbers are small, the investigators concluded with reasonable assurance that x-ray pelvimetry was beneficial in the management of pregnant patients.

In order to quantify benefit versus risk it is necessary to make the kind of determination as illustrated above. However, this is only the first step in such an evaluation. The unknown risk, for example, that a child might develop leukemia several years after being irradiated in utero must be weighed against the known hazard of mortality at birth or during the neonatal period. The risk of leukemia appears very small whereas the hazard of mortality at birth appears to be finite. The sequelae of neonatal asphyxia in those who survive must be weighed against the risk, although small, of leukemia or other effects of radiation. Thus a choice between life for its own sake as

TABLE 8

Organ	Agent	Amount	Radiation Dose				Ref.
			Bone Marrow	Gonad	Organ	Whole Body	
Lung	^{99m}Tc-MAA	3.5 mCi I.V.	70	1M 2F	900	—	10
	^{131}I-MAA	350 uCi I.V.	700	700	1,500	700	10
	^{133}Xe	30 mCi I.V. (U of M protocol)	7	7	255	7	14
Brain	^{99m}Tc-pertechnetate	10 mCi I.V.	150	120M 180F	60	150	11, 12
Kidney	^{131}I-Hippuran	300 uCi (renogram)	18-60	15-60	30-300	18-60	11
	^{99m}Tc-DTPA	3 mCi I.V. (GFR clearance)	60	30-60	120	60	11
Liver	^{99m}Tc sulfur Colloid	3.5 mCi I.V.	200	50M 75F	700	70	10, 11
Placenta	^{99m}Tc-albumin	1 mCi I.V.	10-20	40	28	10-20	11, 12
	^{99m}Tc-pertechnetate	1 mCi I.V.	10-20	40	—	10-20	11
	^{131}I-Albumin	50 uCi I.V.	—	15	40-150	—	11
Bone	^{85}Sr	100 uCi I.V.	4400	2300	4400	2300	11
	^{18}F	1 mCi I.V.	180-230	73	180-230	73	11
	^{99m}Tc-polyphosphate	10 mCi I.V.	300	375M 400F	450	—	8, 12

opposed to quality of life must also be considered. By carefully working one's way through such determinations, decisions on benefit versus risk might be made; however, oftentimes these determinations are well beyond the wisdom or knowledge of individual Nuclear Medicine physicians.[10]

Selected Radioisotopic Procedures to Illustrate Benefit and Risk

Lung

To provide a perspective of the benefits derivable from the practice of Nuclear Medicine, procedures associated with the evaluation of several organs are considered in the paragraphs that follow. A summary of typical radiation exposures for these procedures is shown in Table 8. The first to be considered is the lung which may be studied in a variety of ways using radioactive particles as was considered earlier, or with aerosols or gases (Table 9). Scintigraphy of the lungs, following administration of macroaggregated or microspheres or albumin has become an accepted technique for assessing the distribution of blood flow to the lungs which will be altered in patients with pulmonary emboli and/or obstructive lung disease. Macroaggregates of albumin (MAA) labeled with 131-Iodine were introduced independently by Taplin and Wagner in 1963 for these studies of pulmonary blood flow.

TABLE 9
Radioisotope Evaluation of the Pulmonary System

A.	**Perfusion Scintiphotography with Particles**
	1. Detection of pulmonary thromboembolism
	2. Quantitative evaluation of the distribution of infectious, obstructive and other pulmonary diseases
	3. Evaluation of lung masses
	4. Quantitation of pulmonary venous hypertension
	5. Detection of cardiac disease, i.e., right to left shunts
B.	**Aerosol Inhalation Scintigraphy**
	1. Evaluation of bronchiolar patency and ventilation
	2. Detection of carcinoma of the lung
C.	**Perfusion Scintiphotography with Xenon Gas**
	1. Detection of pulmonary thromboembolism
	2. Evaluation of congenital cardiopulmonary disease
	3. Detection of pulmonary venous hypertension
D.	**Ventilation Scintiphotography with Xenon Gas**
	1. Distribution of inhaled gas and/or washout
	2. Measurement of regional V/Q ratios
	3. Monitoring the Rx of thromboembolism
E.	**Transmission Scintiphotography**
	1. Evaluation of ventilation
	2. Evaluation of pericardial effusion
	3. Evaluation of lung masses
F.	**Miscellaneous**
	1. Evaluation of regional ciliary action
	2. Evaluation of phagocytosis

Since that time, this agent, together with several others, including 99m-Tc MAA, 99m-Tc serum albumin microspheres (SAM) as well as hydroxides formed using 113-In, have been used. At the present time, the agent of choice appears to be 99m-Tc SAM, or MAA which are commercially available in kit form. These radioactive particles are trapped in the pulmonary arteriolar or capillary bed downstream from the site of intravenous injection. On the assumption that complete mixing occurs in the passage through the heart, the amount of radioactivity retained in any given region of the lung is proportional to blood flow to that region.

It is clearly evident that the introduction of these particles to produce vascular occlusions is nonphysiological. Despite this potential problem, this technique has become widely accepted since normally only a very small percentage of the total number of pulmonary arteriolar and capillary units become occluded, and then only for a limited time (clearance half time of six to 20 hours). It has been estimated that the number of arteriolar and capillary units in the human body are approximately 30 million and 280 billion respectively. The numbers and sizes of particles are somewhat variable with as many as 500,000 of the smaller particles (10 to 30 microns and approximately half this number of the larger particles) (50 to 100 microns) administered in those studies.

Adelstein has discussed the benefit versus risk factors for lung scanning to detect pulmonary emboli.[10] He accepted the linear extrapolation from high radiation dose data to determine effects of 70 to 100 millirad to radiation to the bone marrow from the lung scan. From this extrapolation such a patient suffers a three per 1 million risk in acquiring leukemia (above and beyond his normal risk in contracting the disease). Assuming that the mortality for untreated pulmonary embolism is 20% whereas the mortality drops to 5% for those receiving treatment for pulmonary embolism, the salvage made possible by detection and treatment is 150 per 1,000 patients. If the scan is responsible for the initiation of the treatment in only one out of 50 patients examined for pulmonary embolism, the salvage value of three per thousand is achieved, which is 1,000 times greater than the risk of leukemogenesis from a scanning procedure, giving in this case a benefit-risk ratio

of 1,000 to one. This would appear to be an acceptable benefit to risk ratio. However, there are other questions which must be asked. One such question is whether or not the lung scan is essential to the diagnosis. The scan is only one of a battery of tests for pulmonary embolism; but in the experience of many, it can be decisive. Its value appears greatest to those patients who have clinical symptoms of emboli, a normal chest roentgenogram, and appear clinically ill. Certainly the lung scan would be of diagnostic value in these patients to determine whether or not hospitalization is indicated.

Because of several causes for non-uniform pulmonary blood flow other than pulmonary emboli, it is necessary to employ studies which measure ventilation directly. This may be accomplished either by inhalation of aerosol or radioactive gases. Satisfactory radioaerosol inhalation scintiphotography is difficult to perform because of problems in achieving particles of uniform size below two microns, which can readily pass into distal portions of lung. Furthermore, unless extreme care is exercised, significant radioactive contamination of the immediate environment presents a significant radiation hazard. Thus, more and more attention is being given to the use of a radioactive gas. The only radioactive gas which is currently available in quantity and has reasonable characteristics for use in external counting is 133-Xenon. Using techniques developed in our clinic which involve the use of single or dual scintillation camera arrangements together with a dedicated computer, it is possible to provide rather specific information on both regional ventilation and regional blood flow. This is of important physiological significance, inasmuch as there must be a balance between regional ventilation and perfusion (ventilation-perfusion ratios) in order to provide adequate gas exchange. Details of the utilization of the technique in the study of patients with a wide variety of pulmonary disorders has been published to indicate patient benefit at a relatively small risk.[15-18]

Brain

Radioisotopic techniques for evaluation of the central nervous system are among the most widely accepted procedures available in the current practice of Nuclear Medicine. A summary of the radioisotopic evaluation of this system is shown in Table 10. Of the procedures performed, the brain scan is the most common and is usually performed following a careful history and physical examination in the evaluation of a patient with suspected intracranial disease. The negligible morbidity associated with brain scanning compared to other techniques such as angiography and pneumoencephalography for the evaluation of this organ, has contributed significantly to its great popularity. The relative accuracies of these techniques for the detection of brain pathology are quite comparable.[19,20] In some instances, the location and appearance of a lesion (usually an abnormal increase in radioactivity), interpreted with the knowledge of clinical history, allow a definitive diagnosis to be made with rather high probability. An example of this is the conversion from a normal to abnormal scan appearance in the distribution of one of the major cerebral arteries within days after a cerebral vascular accident. In addition, accurate anatomical localization can be achieved. This may be of great value in guiding the surgeon in his approach to a brain lesion. A wide variety of agents have been employed in the performance of brain scans. At present 99m-Tc as pertechnetate is the tracer that best satisfies the desirable characteristics of a radionuclide used for brain scanning. This agent provides a higher photon flux at a lower radiation exposure than is obtainable with the other brain scan agents.[19,20]

It must be recognized that the brain scan is complementary to radiographic examinations (cerebral arteriogram and pneumoencephalogram) in the detection of brain pathology. Because the brain scan tends to be noninvasive, provides an accuracy comparable to radiographic techniques ($> 90\%$) and can be performed with significantly less radiation dose, it serves as the appropriate screening technique.

TABLE 10
Radioisotopic Evaluation of the Central Nervous System*

1. Screening and characterization of primary brain tumors
2. Detection of cerebral metastases
3. Measurement of cerebral blood flow
4. Detection of cerebral abscesses
5. Detection of trauma (intracerebral hemorrhage, subdural hematoma, superficial and deep contusions)
6. Detection of cerebrospinal fluid fistulae
7. Evaluation of shunts in the treatment of hydrocephalus

*Adapted from Wagner.

Kidney

As with the evaluation of both the pulmonary and central nervous systems, there are a wide variety of procedures in Nuclear Medicine which might be employed in evaluation of the kidney and urinary system (Table 11). Each of these procedures requires special consideration of radioisotopes used.[21] Because of the relatively short biological half-life of most radioactive agents used, the radiation dose is usually considerably less than that delivered using techniques of Diagnostic Radiology (Table 8).[12] Furthermore through the use of computers or other data storage devices as part of the Nuclear Medical instrumentation, it is possible to obtain quantitative information on specific renal parameters such as glomerular filtration rate, or tubular function and renal plasma flow. Despite the exquisite sensitivity of most Nuclear Medical tests of renal function, great care must be exercised if the data are to be relied upon. Such things as hydration status, blood pressure and patient position must be carefully controlled. There seems to be little doubt that the benefits exceed the risk by many orders of magnitude in Nuclear Medical studies of the kidney and urinary system if these studies are carefully performed and evaluated.

TABLE 11
Radioisotope Evaluation of the Kidney and Urinary System

1. Renal Perfusion
   a. Differential renal blood flow
   b. Vascular anomalies (aneurysms, malformations)
   c. Arterial-venous transit time
2. Renal Function (Renogram)
   a. Glomerular filtration rate
   b. Tubular function
   c. Renal plasma flow
   d. Outflow obstruction
   e. Renal transplant rejection
3. Renal Scintigraphy
   a. Size
   b. Shape
   c. Location (ectopia)
   d. Polycystic disease
   e. Trauma
   f. Tumor
   g. Function
   h. Hydronephrosis
4. Ureteral reflux
5. Voiding cystogram
6. Residual urine

Liver

Liver is a common site of both primary diseases and tumor metastases. It is extremely difficult to examine this organ by palpation or by most conventional radiographic techniques. On the other hand, the liver can be readily visualized by the administration of radiopharmaceuticals which will label either the parenchymal (polygonal) or the reticuloendothelial cells (See section on Choice of Radiopharmaceuticals). The polygonal cells constitute 60% of the liver mass and are responsible for the metabolic functions associated with the liver. The reticuloendothelial (Kupfer) cells account for the remaining 40% of liver mass and are primarily associated with phagocytosis. Both cell populations are closely intermingled and cannot be segregated on a macroscopic anatomic basis. An important "third population compartment" exists in the diseased liver and may consist of metastatic tumor, fibrotic reactive elements, blood or even such noncellular components as fluid or pus.

TABLE 12
Radioisotopic Evaluation of the Skeletal System

1. Pre-operative evaluation of patients with primary neoplasm, especially of the breast, prostate or lung
2. As an aid in planning radiation therapy
3. Evaluation of bone pain in a patient without demonstrable radiographic abnormality
4. Evaluation of therapy in Paget's disease of bone
5. Evaluation of bone in suspected osteomyelitis
6. Evaluation of the effect of trauma not otherwise revealed by radiography
7. Early detection of avascular necrosis

Radiopharmaceuticals normally used for evaluation of the liver (with the possible exception of ^{67}Gallium) label normal cellular components of the liver. Thus, abnormal areas within the liver are "filling defects" in the liver scan. The ability to visualize these defects depends on both their size and their location within the liver substance. Thus the overall diagnostic accuracy in liver scanning tends to be somewhat below that enjoyed in procedures such as the brain scan in which the abnormal foci selectively concentrate the radiopharamaceuticals. Nonetheless, the procedure is essentially without morbidity and using an agent such as 99m-Tc Sulfur colloid, the radiation dose appears to be quite acceptable (Table 8). As a first step screening procedure of the cancer patient, the liver scan has become standard practice. Because of the importance of evaluating both liver function and liver morphology prior to definitive treatment of the patient with or suspected to have cancer, the relatively low risk from radiation appears wholly justified.

Placenta

All physicians agree that radiation in any form

should be avoided if at all possible during pregnancy. However, the clinical information that might be obtained may be of critical importance in determining, for example, the mode of fetal delivery. This information may be provided from either Nuclear Medical or Radiological techniques. The situation is not too different from the problems studied by physicians in South Africa who were concerned about radiation delivered in cephalopelvimetry.[10] If one considers the management of a patient with vaginal bleeding in the third trimester of pregnancy, the advisibility of some radiation exposure for diagnostic information is readily understood. Approximately 4% of all obstetrical patients have some bleeding in the last trimester of pregnancy. Without definitive treatment, approximately 25% of all cases of fetal death lie within this group. Thus the diagnoses of causes of third trimester bleeding are important with the two most common causes being: premature separation of the placenta and placenta previa.

To make the diagnosis of placenta previa, the exact location of the placenta within the uterus is mandatory and can best be accomplished by radioisotope placentography using 99m-Technetium as pertechnetate or labeled to albumin, and a scintillation camera. Other indications for placental localization include the evaluation of certain malpresentations of the fetus and to determine the best approaches to the intervillus space and amniotic fluid cavity prior to such procedures as amniocentesis. It must be recognized as with most other Nuclear Medicine procedures, that radioisotope placentograms are oftentimes complementary to radiologic techniques in evaluation of placental location. However, because the Nuclear Medical techniques deliver significantly less fetal radiation dose than do radiographic techniques, the former should be employed first (Table 8).[12] If additional studies appear necessary they may then be instituted.

Bone

Although bone scanning has been performed for many years, it was only recently that this technique has assumed a major role in the practice of Nuclear Medicine. This major stride was made possible by the introduction of a polyphosphate complex that acted as a bone seeking agent and to which technetium-99m was attached as a radioactive tracer. This agent or similar agents, such as pyrophosphate or diphosphonate, with a technetium label may be administered in millicurie amounts to permit the skeletal system to be viewed in its entirety.

It is well known that the resolution obtainable by bone scanning is inferior to that from conventional radiography. Nonetheless, bone scanning is considered advantageous because it has been shown that this procedure can show abnormalities in the skeleton long before they might be appreciated on the roentgenograms.

Most bone scans are performed as part of a search for metastatic cancer. However, the underlying principle in the uptake of tracer material relates to the attempt of bone to repair itself and as a result, bone scanning is not specific for tumor. Any insult to the integrity of bone results in some degree of destruction which in turn stimulates the formation of an osteoid matrix. In addition many of these processes result in hyperemia which presents an increased quantity of radioactive tracer to the area of abnormality.

Intelligent and efficient use of bone scanning demands that findings be interpreted in context with appropriate information available from the patient's history, physical findings and laboratory data. It may be summarized that areas in which bone scanning is most useful are shown in Table 12.

It may be concluded from the wide range of diagnostic possibilities as shown in Table 12, that bone scanning is truly an important entity in the practice of Nuclear Medicine. The radiation dose of 300 to 400 millirads to bone marrow, gonads and the total body from 10 millicuries technetiated compound appears to be an acceptable radiation risk because of the important clinical information that might be obtained. It should also be recognized that the radiation dose from this procedure is comparable to each radiograph of a portion of the skeleton. In a total skeletal survey by radiographic means, the overall radiation dose would be significantly greater than using the radioisotopic method.

Summary

Uses of radioisotopes in the practice of medicine have increased several fold during the past two decades leading to the establishment in 1972 of certification in the specialty of Nuclear Medicine by the National Board of Medical Examiners.

An overview of radiation exposures to patients undergoing Nuclear Medicine procedures has been presented along with considerations of benefits that patients might derive from having had these procedures performed. Specific reference has been made to representative procedures in which specific radiopharmaceuticals are administered to patients. The radiation dose to patients is shown to be quite low for most procedures, almost always less than that delivered during comparable radiologic procedures.

The risk from low doses of radiation has been conservatively estimated by extrapolating to zero dose from data on radiation effects observed at high dose levels. Thus, this conservative estimate represents the maximum risk, with the actual risk likely to be considerably below this value. This fact has been substantiated in many experiments in radiation biology in which a radiation dose has been delivered using several fractionated smaller doses, allowing for repair and recovery between each dose and thus reducing the radiation effect from that which would have occurred had the radiation been delivered acutely.

For cephalopelvimetry and for lung scanning for pulmonary emboli, the quantitative determination of benefit to risk ratio has been developed. Although this approach is very desirable and provides much needed information, it is exceedingly difficult to establish benefit verus risk ratios in absolute terms. Thus, good clinical judgment must be employed in practice of Nuclear Medicine just as it should be employed in all aspects of medical practice. We believe that radioisotopes used judiciously in the practice of Nuclear Medicine provide benefits that far outweigh the potential risks associated with the small amount of radiation exposure involved.

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Minnesota Radiological Society

Winter Meeting, February 1, 1975, Minnesota Club, St. Paul, Minnesota—8:00 P.M.

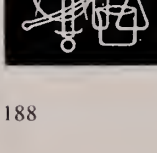
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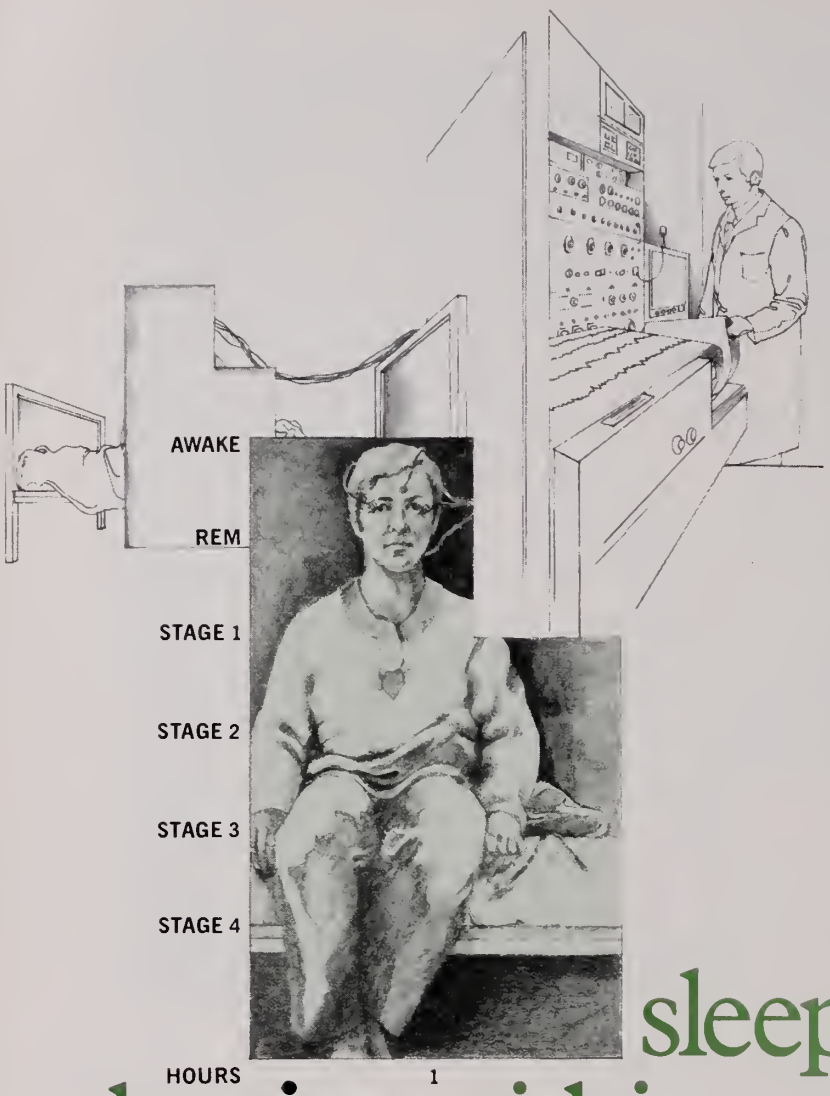
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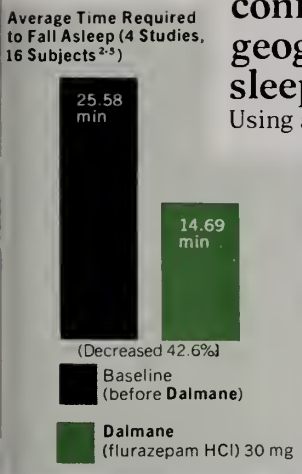
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Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

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REFERENCES: 1. Kales A, *et al*: *Arch Gen Psychiatry 23*:226-232, Sep 1970
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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

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TO KEEP BLOOD PRESSURE DOWN AND KEEP POTASSIUM LEVELS UP



Editorials

First A Physician

THIS SPECIAL ISSUE OF MINNESOTA MEDICINE is dedicated to the memory of the late Doctor Karl Wilhelm Stenstrom, who was loved and revered as a humanitarian, oncologist, teacher, and leader as well as a physicist. Although without a medical degree, he was a physician in the true sense of the word.

While purusing the scientific papers published here, we cannot but be impressed by the technological advances made in recent years. More importantly, however, these articles brought out that the radiologist's primary concern is the patient, and his basic "weapon" an adequate knowledge in basic and clinical sciences. Our surgical colleagues like to say that a surgeon is a physician who can operate. It should also be said that a radiologist is, first, a physician. We should say that in a manner loud and clear, by word and by deed. It will be none too soon either, because the public and the government have many misconceptions about what a radiologist is, and that threatens to adversely affect the practice of radiology. This situation was driven home to us by Dr. John Coleman at the last meeting of the Minnesota Radiological Society while relating his experience before a subcommittee of the State Legislature.

This special issue would not have been possible without the enthusiastic support and cooperation from the members of the Minnesota Radiological Society and its Publication Committee, and the editors of MINNESOTA MEDICINE. To them and to the authors of the published articles we are deeply indebted.

Shih Hao Tsai, M.D.
Merle K. Loken, M.D., Ph.D.
Guest Editors

Bacterial Infections of the Skin

It is a pleasure to commend to the readers of Minnesota Medicine the recent article on "Bacterial Infections of the Skin" by Paul R. Vandersteen, M.D.* This communication is cogent, succinct, and complete. The references are pertinent and point to both established and current investigations regarding the microbiology of cutaneous diseases.

Of special interest to Minnesota physicians is the investigations of Lewis W. Wannamaker, M.D., Professor of Pediatrics and Microbiology at the University of Minnesota Medical School, and his coworkers, Adnan S. Dajani, M.D. and Patricia Ferrieri, M.D.[1,2] Their work has established new insights into the natural history, microbiology, serology, and epidemiology of an old disease, impetigo contagiosa. First, there are two distinct clinical forms of impetigo: (1) bullous impetigo, associated with phage group II staphylococci, the lesions of which form a varnish-like crust after the bullae rupture and (2) vesicular impetigo, associated with group A beta-hemolytic streptococci or a mixture of streptococci and staphylococci, the lesions of which form thick, adherent, honey-colored crusts after the vesicles rupture.

The results of the studies of these authors have failed to support the view that the upper respiratory tract is an important source of streptococci that cause impetigo. Indeed, their prospective studies[1,2] have demonstrated different patterns of migration from one site to another for the two bacterial species: for the staphylococci the site sequence is respiratory tract, normal skin, and lesions; for the streptococci, normal skin, lesions, and respiratory tract. Thus, for both species, the normal skin is colonized before the skin lesions develop. Furthermore, the streptococcal serotypes are different for the organisms found in impetiginous lesions from those in upper respiratory infections.

Acute poststreptococcal glomerulonephritis is one of the most serious complications of streptococcal impetigo. A three-week latent period between the appearance of impetiginous lesions due to a nephritogenic strain and the development of acute glomerulonephritis provides a theoretical opportunity to abort this complication with penicillin therapy. There have been no controlled, prospective studies that indicate the efficacy of such therapy and clinical reports indicate that renal complications may eventuate, despite penicillin therapy.

We all look forward with eager anticipation to controlled, prospective studies designed to answer some of the vexing problems of complications following streptococcal impetigo.

Roy S. Rogers III, M.D.†
Rochester, Minnesota

*October issue, MINNESOTA MEDICINE, page 838.

†Department of Dermatology, Mayo Clinic and Mayo Foundation.

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Acne: Pathogenesis and Treatment

In the October issue of Minnesota Medicine* Mescon and Kohn presented a brief current review of the pathogenesis and therapy of acne vulgaris. Understanding pathogenesis provides a more rational basis for the various modalities used to treat this complex and distressing disease.

Acne is now recognized as a disease of pilosebaceous dysfunction which affects virtually all adolescents or young adults through a wide spectrum of severity. Because no simple therapy is consistently effective and acne is common, self-limited, and not a threat to life, many parents, teenagers, and physicians tend to accept acne as a "fact of life" which must be tolerated as a part of achieving adulthood. This attitude may lead to inadequate therapy or neglect with occasionally damaging or disastrous effects on the short and

*See page 788.

long term emotional health of the affected boy or girl.

Although acne cannot be prevented or cured, much can be done to control it. A well planned, aggressive program of selected topical and, if indicated, systemic therapy should be based on an understanding of the nature of the disease and aimed at the specific lesions present. Improvement of the patient's daily appearance and minimizing permanent scarring are realistic goals of therapy.

Because emotional problems are generated by this disfiguring disease, special attention should also be given to the fears and anxieties of young people with acne. Time should be spent to discuss with patients what is known about acne and how this relates to their therapy. Unspoken questions regarding the erroneous associations of acne with such things as sexual habits or feelings, venereal disease, poor hygiene, bad eating habits or constipation can be answered by voluntary reassurance from an understanding physician. All these measures combined should minimize any permanent physical or psychological scarring that might result from this still perplexing disease.

Dennis D. Knutson, M.D.*
Rochester, Minnesota

*Mayo Clinic and Mayo Medical School.

End Stage Renal Disease

IN THIS COUNTRY renal transplantation and chronic dialysis are now well accepted alternatives for the patient with end-stage renal disease. Since July of 1973 the Federal Government has underwritten the major portion of the costs of treatment connected with renal transplantation and chronic dialysis.

At the present time renal transplantation or dialysis in this country requires an institutional approach to provide all of the varied expertise needed to support the many medical needs of the patient.

The Upper Midwest is very fortunate in having four independent but cooperating centers. As a result there are adequate facilities so that no patient who wants therapy has to be denied.

Although dialysis and transplantation are both alternatives to the patient with terminal renal failure, they are in no way comparable except that they are both lifesaving procedures. They differ markedly in quality of life. At best a renal transplant can offer a patient near normal health. Except for daily medications and "regular checkups" they have no limitations because of the transplant. Once the early post transplant period is passed, eg. one year, the loss rate for kidney or patient is low. The average cost for yearly maintenance is not great. Chronic dialysis on the other hand, in its present state usually requires confinement to a treatment area three times a week for six to 10 hours at a time. The cost of these treatments is great even if done at home. The patient on chronic hemodialysis is frequently faced with many ongoing problems such as those with vascular access or dializer problems as well as a host of possible medical problems.

Quality of life especially as seen by the patient should be important in deciding what form of treatment to use.

Dr. Kjelstrand et al.* in the article "Renal Transplantation at the University of Minnesota" reports the progress and results of the largest renal transplant program in existence now. The results are good. It is because of results such as shown by Dr. Kjelstrand that the primary goal in treating most terminal renal failure patients should be in evaluating the patient and his family for a renal transplant. Not all patients are able to have a transplant as the authors point out. It is for these people and those awaiting a kidney from a cadaver source that chronic dialysis should be used.

Finally, all institutions doing renal transplantations in the Upper Midwest have the ability to rapidly travel great distances to obtain kidneys for transplantation. Therefore, community physician participation in realizing our needs is becoming increasingly important. Information concerning the program can be obtained quickly day or night by calling any of the transplant or renal services, or the Kidney Foundation of the Upper Midwest.

Robert C. Andersen, M.D.
Hennepin County General Hospital

*See page 886, November issue, MINNESOTA MEDICINE, 1974.

Urinalysis, The Invaluable Laboratory-Clinical Profile

GOD BLESS Urinologists!

Dr. Wilson's paper* in the January issue of MINNESOTA MEDICINE is an excellent review of renal physiology, renal function tests, and urinalysis with proper emphasis on the pitfalls of some old and new renal function tests and the fallacy of urinalysis without microscopy. For the effort, time, and expense expended, urinalysis probably yields more clinically helpful data than any other laboratory test. Yet, as is true of many "routine" laboratory procedures, the maximum benefit is often not utilized by the clinician.

Simultaneous serum and urine osmolality measurement is one of the best but least utilized renal profiles. Thirty hour dehydration and routine urine osmolalities are generally impractical and not necessary. Selected simultaneous urine and serum osmolality after 14 hours of dehydration is a sensitive, practical and frequently invaluable renal function test. After a 14-hour fluid fast, a normal urine osmolality is 850 m Osm/Kg water or more and the urine to serum osmolality ratio is 3.0 or greater. This test is perhaps the most sensitive indicator of pyelonephritis. A urine to serum osmolality ratio is also very helpful in predicting the significant renal insufficiency following shock. A ratio of 1.5 or less is presumptive evidence of progressive renal disease; a ratio over 1.5 would make the likelihood of significant renal damage remote.

Abnormal proteinuria, as Wilson relates, may be difficult to define. Though adult patients with 24-hour excretions of 150-500 mgm. (perhaps even higher) protein have a high incidence of glomerular abnormalities, the significance of this is obscure. If one includes focal foot process fusion as an index of glomerular disease, the statistics are misleading. Some (focal) foot process fusion is almost always present and generally increases with the degree of proteinuria (i.e., foot process fusion is predictable without biopsy when significant proteinuria is detected). If 150-500 mgm. proteinuria is the *only* abnormality disturbing the *physician,* invasive techniques usually are not valuable, at least for the *patient.* Minimal morphologic changes may pacify some immediate "diagnostic" goals, but therapy is almost never indicated for the otherwise normal patient with "proteinuria" of this degree. Proteinuria is sometimes just proteinuria, and not an indication of disease.

Hematuria plus proteinuria, identification of light chain proteinuria, and nephrotic proteinuria are different stories, per Wilson. Isolated nephrotic (2 grams/24 hours in the adult) proteinuria is, of itself an indication for biopsy, following proper clinical considerations of possible etiology. If Lipoid Nephrosis or Lupus Nephritis are the diagnostic considerations, the patient's therapy and prognosis are directly affected by biopsy results.

Wilson aptly points out that urinalysis must be done on a properly collected, fresh specimen. This cannot be overemphasized. A urinalysis report on an alkaline urine should always be viewed with great skepticism, especially in a hospital setting. If a clinician is interested in a specific aspect of a urinalysis, he should make certain of a properly collected specimen for that parameter; e.g., if one is interested in diagnosis of a renal tubular acidosis syndrome, one should personally make certain that the pH is done on a *freshly* voided specimen.

As documented, there is no substitute for *good* urine microscopy.† Through microscopic review of a fresh concentrated specimen is the most valuable part of the "routine" urinalysis despite the mundane aura that continues to invest the task.

Wilson's report of a simplified isotopic test for glomerular filtration rate is provocative, and sounds as though it could be a practical approach for replacement of the now popular endogenous creatinine clearance which is subject to error. Despite the limitations, creatinine clearance is most practical, universally available and reliable *when proper specimen collection is obtained.*

Wilson chooses to exclude discussion of the P.S.P. as a renal function test or the indications for Addis counts. Amen. May they rest in peace.

Martin A. Segal, M.D.†
Abe L. Fox, Jr., M.D.

*See page 9.

†Founder of S.P.P.U. (Society for the Promotion of Prestige of Urinalysis).

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The Role of the Detail Man

Opinion & Dialogue



Dr. Willard Gobbell
Family Physician
Encino, California

"I may be prejudiced, but I an very much in favor of the detail me I meet. Most of them are knowledg able about the drugs they promote and can be a great help in acquaint ing me with new medication."

Family Physician's Perception

I think that most general practitioners in this area feel as I do about the detail man. Over the years I have gotten to know most of the men who visit me regularly and they in turn have become aware of my particular interests and the nature of my practice. They, therefore, limit their discussion as much as possible to the areas of interest to me. Since I usually see the same representative again in future visits, it is in his best interest to supply me with the most honest, factual, as well as up-to-date inforrnation about his products.



Dr. Jeremiah Stamler
Chairman
Department of Community Health and Preventive Medicine, and Dingman Professor of Cardiology
Northwestern University Medical School

"In the total picture of dealing with health problems in this counti there is a potential for detail men to play a meaningful role."

The Positive Influence

My contact with representatives and salesmen of the pharmaceutical industry is the type of contact that people in a medical cente research people, and academic people have and that's in all likelih on a somewhat different level from that of the practicing physician.

Let me touch on how I person ally perceive the role of the sales representative. These men reach large numbers of health professionals. Thus they could be—and at times actually are—disseminators of useful information. They could consistently serve a real edu cational function in their ability to discuss their products.

At present they do distribute printed material, brochures and pamphlets—some of it scientifically sound and therefore truly useful—as well as some excellent film produced by the pharmaceutical industry. When they function in thi

He a Source of Information?

Yes, with certain reservations. The average sales representative has a great fund of information about the drug products he is responsible for. He is usually able to answer most questions fully and intelligently. He can also supply reprints of articles that contain a great deal of information. Here, too, I exercise some caution. I usually accept most of the statements and opinions that I find in the papers and studies which come from the larger teaching facilities. It goes without saying that a physician should also rely on other sources for his information on pharmacology.

Training of Sales Representatives

Ideally, a candidate for the position as a sales representative for a pharmaceutical company should be a graduate pharmacist who has a questioning mind. I don't think this is possible in every case, and so it becomes the responsibility of the pharmaceutical company to train these individuals comprehensively. It is of very great importance that the detail man's knowledge of the product he represents be constantly reviewed as well as updated. This phase of the sales representative's education should be a major responsibility of the medical department of the pharmaceutical company.

I am certain that most of these companies take special care to give their detail men a great deal of information about the products they produce—information about indications, contraindications, side effects and precautions. Yet, although most of the detail men are well informed, some, unfortunately, are not. It might be helpful if sales representatives were reassessed every few years to determine whether or not they are able to fulfill their important function. Incidentally, I feel the same way about periodic assessments of everyone in the health care field, whether they be general practitioners, surgeons or salesmen.

Value of Sampling

I personally am in favor of limited sampling. I do not use sampling in order to perform clinical testing of a drug. I feel that drug testing should rightly be left to the pharmacology researcher and to the large teaching institutions where such testing can be done in a controlled environment.

I do not use samples as a "starter dose" for my patients. I do, however, find samples of drugs to be of value in that they permit me to see what the particular medication looks like. I get to see the various forms of the particular medication at first hand, and if it is in a liquid form I take the time to taste it. In that way I am able to give my patients more complete information about the particular medications that I prescribe for them.

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pacity they are indeed useful; rticularly in the fact that they seminate broadly based educa- hal material and serve not just 'pushers" of their drugs.

Other Side of the Coin

Obviously, the pharmaceuti- companies are not producing all s material as a labor of love— y are in the business of selling ducts for profit. In this regard ambitious and improperly moti- ed sales representative can rt a negative influence on the cticing physician, both by pre- ting a one-sided picture of his duct, and by encouraging the ctitioner to depend too heavily drugs for his total therapy. In se ways, the salesman has often torted objective reality and termined his potential role as an cator.

Industry Responsibility

Since the detail man must be nformation resource as well as presentative of his particular rmaceutical company, he uld be carefully selected and thoroughly trained. That training, perforce, must be an ongoing one. There must be a continuing battle within and with the pharmaceutical industry for high quality not only in the selection and training of its sales representatives, but also in the development of all of its promotional and educational material.

The industry must be ready to accept constructive as well as corrective criticism from experts in the field and consumer spokesmen, and be willing to accept independent peer review. The better educated and prepared the salesman is, the more medically accurate his materials, the better off the pharmaceutical industry, health professionals and the public—*i.e.*, the patients—will be.

Physician Responsibility

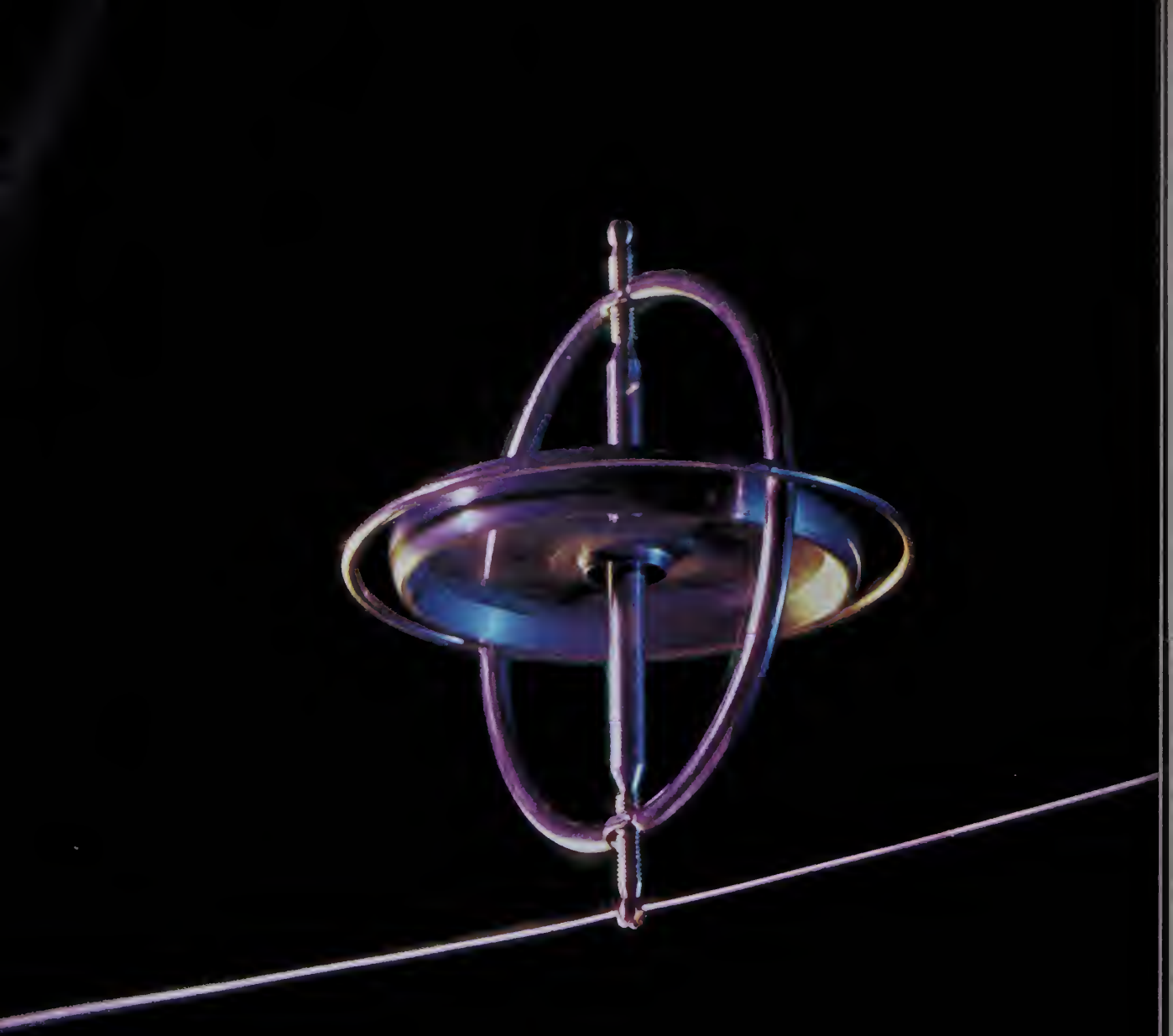
The practicing physician is in constant need of up-dated information on therapeutics, including drugs. He should and does make use of drug information and answers to specific questions supplied by the pharmaceutical representative. However, that information must not be his main source of continuing education. The practitioner must keep up with what is current by making use of scientific journals, refresher courses, and information received at scientific meetings.

The practicing physician not only has the right, but has the responsibility to demand that the pharmaceutical company and its representatives supply a high level of valid and useful information. I feel certain that if such a high level is demanded by the physician as well as the public, this demand will be met by an alert and concerned pharmaceutical industry.

From my experience, my impression is that sectors of the pharmaceutical industry are indeed ethical. I challenge the industry as a whole to live up to that word in its finest sense.

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Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of ove mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show palate. Congeners of meclizine have caused cleft palate in species other than th

Meclizine HCl is contraindicated in individuals who have shown a pre hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this patients should be warned of this possibility and cautioned against driving a operating dangerous machinery.

Usage in Children. Clinical studies establishing safety and effectiveness in ch have not been done; therefore, usage is not recommended in the pediatric age

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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Scan Conference

"Large Heart"

A tweny-five-year-old male was admitted to the hospital complaining of crushing chest pain associated with shortness of breath. These symptoms had been present for about three weeks.

Six years before this admission he received a kidney transplant because of renal failure secondary to chronic glomerulonephritis. Late rejection of the transplanted kidney required nephrectomy two months before admission. He has been on renal dialysis since that time.

On physical examination, the examiner found an irregular pulse of 100, blood pressure of 110/70 mm Hg., paradoxical for 30 mm. The heart sounds were distant and there was no rub.

A chest Xray at this time (Figure 1) exhibited the lungs to be clear with no evidence of vascular engorgement or edema. The cardiac silhouette was markedly enlarged. A radionuclide angiogram was performed. The static phase image of the heart obtained at the conclusion of this study is shown in Figure 2.

What is your diagnosis? (See next page.)



Fig. 1—Chest Xray. Large cardiac silhouette. Lung fields clear.

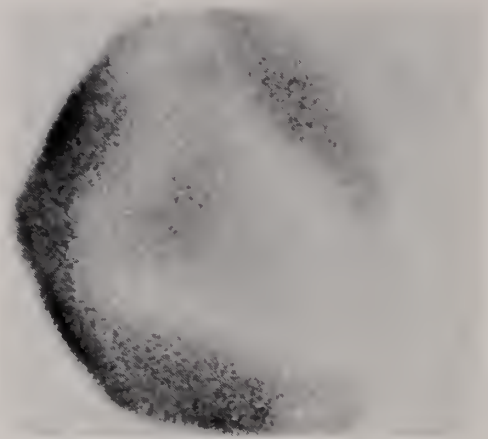


Figure 2—Cardiac blood pool image obtained after injection of 10 mCi ^{99m}Tc-pertechnetate.

Diagnosis: Massive Pericardial Effusion

Shortly after completion of the radionuclide angiogram, pericardiocentesis was performed yielding 1750 cc. of bloody fluid. The patient showed immediate improvement in his clinical condition. Culture of the fluid proved to be sterile.

The classical physical findings of pericardial effusion are well known and helpful when present. Frequently the only findings may be an enlargement of the cardiac silhouette on the chest Xray and it is necessary to resort to one of many means of investigation to distinguish between an enlargement of the cardiac chambers and a pericardial effusion. Current methods use intravenous CO_2, positive contrast angiography, radionuclide angiography and blood pool scanning and ultrasound.

Radionuclide angiography is a non-invasive technique which is simple to perform, not requiring elaborate equipment beyond that which is now very widely found in Nuclear Medicine Departments.[1,5] The technique depends upon the identification of the cardiac blood pool and comparison of the size of this pool to the cardiac silhouette. In Figure 3 the activity within the heart is identified in the center of a large region of diminished activity. This latter region corresponds to the enlarged "cardiac silhouette" as seen on Xray. Thus, the presence of a fluid filled pericardium is demonstrated as a "halo" surrounding the heart. If the

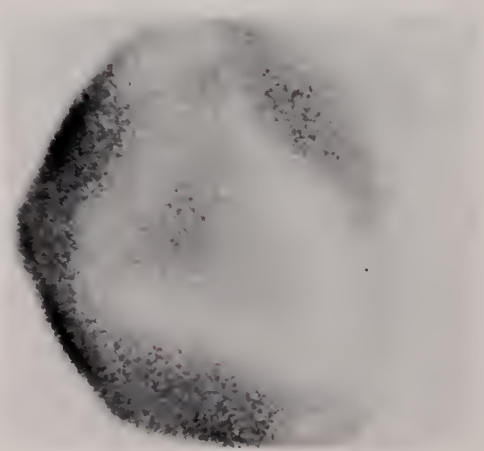


Fig. 3(a)—Cardiac blood pool image.

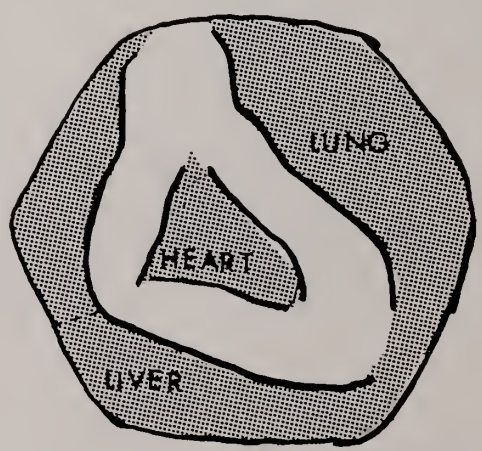


Fig. 3(b)—Diagram of Figure 3a. identifying activity in heart separated from lungs and liver by "halo" of pericardial fluid.

enlarged cardiac silhouette is due to large dilated cardiac chambers, the area of activity is correspondingly large and the classic "halo" is absent. Unfortunatcly, thc technique is not specific and a thickened pericardium, of any etiology, will produce the same appearance.

Although difficult to achieve, there have been somc attempts at comparison studies of the different techniques available for detection of pericardial effusion.[2,3] Ultrasound techniques, CO_2 injection and positive contrast studies seem to present a greater degree of sensitivity in detecting effusion. However, false positive and false negative results have occurred with all methods.[2-4]

For the present, radionuclide angiography can be performed easily and rapidly. The patient can be in either the recumbent or upright position and there is a very low radiation exposure. The minimal detected quantity of fluid with this method is approximately 200-300 cc.[2,3]

*Associate Professor of Radiology.

Marvin E. Goldberg, M.D.*
University of Minnesota

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Emergency Medical Technicians Course

As of January, 1975, the United States Department of Transportations standard 81-hour course for Emergency Medical Technicians will be offered in East Grand Forks, Moorhead, Wadena, Willmar, Jackson, Hibbing and White Bear Lake, at the Vocational Technical Institutes on an on-going basis.

This has been made possible by a grant from HEW through the Minnesota State Department of Education to VoTech 916 at White Bear. The latter institution developed the program according to D.O.T. guidelines with approval of the Minnesota State Department of Health, and is charged with coordination of training and organizing the distribution of material to the six sites.

Upgrading of the basic skills of EMT personnel is of vital importance. But, in view of the fact that legislation is expected in the near future making this training mandatory for any person involved in ambulance and emergency care, it is even more important that the large number of persons serving in this capacity in Minnesota receive the proper training so that they can be certified in the future.

A course such as the one mentioned needs the support and the participation of the medical profession. Physicians in the above mentioned areas are urged to lend their support and service to the vocational technical institutes. Participation of local physicians is urgently needed to make this type of training a success.

Robert A. van Tyn, M.D.
Chief, Emergency Medicine Dept.
St. Paul Ramsey Hospital
Chairman, Statewide EMT
Governance Committee

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Minneapolis, Minn. 55414
612-331-8216



Putting out the fires of arthritic pain

Rheumatoid arthritis can sometimes spread like wildfire, with joint after joint going up inflamed: "The usual onset is manifested by spotty joint involvement but an acute onset of symmetrical polyarthritis may be noted."*

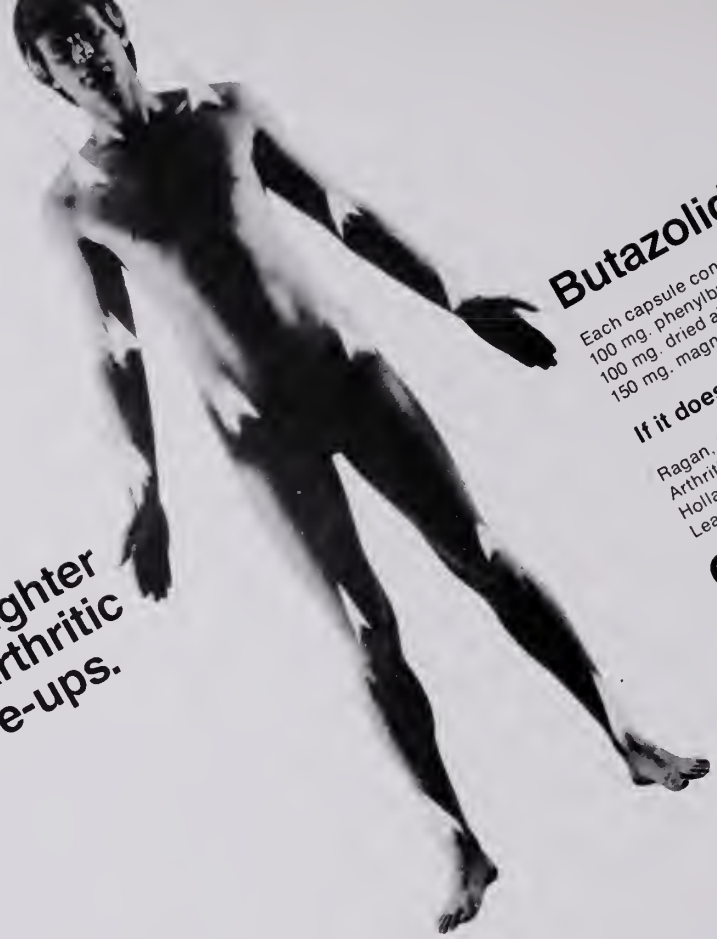
If aspirin fails, consider Butazolidin alka. Giving one capsule four times a day often provides prompt, pain-relieving, anti-inflammatory action to help restore joint mobility. The results you can get within a week can be maintained on as little as one or two capsules daily.

Serious side effects can occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings, contraindications and adverse reactions. For full details, please read the prescribing information. It's summarized on the back of this page.

Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.



Fire fighter for arthritic flare-ups.

Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.

Ragan, C.: The Clinical Picture of Rheumatoid Arthritis, in Arthritis, ed. 8, edited by J. L. Hollander and D. J. McCarty, Jr., Philadelphia, Lea & Febiger, 1972, chap. 21, p. 335.

Geigy

Important Note: This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Substitute alka capsules for tablets if dyspeptic symptoms occur. Patients should discontinue the drug and report immediately any sign of: fever, sore throat, oral lesions (symptoms of blood dyscrasia); dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.

Indications: Rheumatoid arthritis, osteoarthritis, bursitis, acute gouty arthritis and rheumatoid spondylitis.

Contraindications: Children 14 years or less; senile patients; history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia; history or presence of drug allergy; blood dyscrasias; renal, hepatic or cardiac dysfunction; hypertension; thyroid disease; systemic edema; stomatitis and salivary gland enlargement due to the drug, polymyalgia rheumatica and temporal arteritis; patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.

Warnings: Age, weight, dosage, duration of therapy, existance of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.

Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check, pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.

Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy. CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia, ulcerative stomatitis, salivary gland enlargement.

(B)98-146-070-J (10/71)

For complete details, including dosage, please see full prescribing information.

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Special Article

A Successful Academic Partnership K. Wilhelm Stenstrom and the Department of Radiology, University of Minnesota

LEO G. RIGLER, M.D.*

"A good name is rather to be chosen than great riches."

RETURNING IN 1927 FROM a year spent abroad studying radiology, largely in Stockholm, I presented myself at the University Hospital, then still the Elliott Memorial, to begin my first day in a full time position at the University of Minnesota. Almost my first introduction was to a rather slightly built, thin, almost ascetic looking man, with a slight Swedish accent, Professor K. Wilhelm Stenstrom, who was already firmly asconced in the Cancer Institute which had been built during the year I was away. He was a Ph.D. in Physics, was now an associate professor of Bio-physics in the Department of Physiology, and was both the Physicist and the Chief of Radiation Therapy in this new addition to the University Hospital.

Prior to 1927 Dr. Robert Allison was in charge of the radiology work at the University of Minnesota Hospital. He spent a few hours a day at the hospital, the remainder of his time being devoted to his private practice and to other hospitals. To Professor Hilding Berglund, originally from Stockholm, then Chief of the Department of Medicine, this situation was most unsatisfactory. Coming from Sweden, where radiology had a very high place in clinical medicine, he felt that there should be a full time director for the division. I had been the Radiologist for the Minneapolis General Hospital, and at this time, also in private practice. My own concern was largely with diagnosis; radiation therapy at the hospital was extremely limited and of little significance. In my office, however, I was compelled to do some therapy since we had 50 mg of radium in a brass capsule for the treatment of superficial lesions. My training in therapy was rudimentary, almost entirely from textbooks, and my experiences with therapy were not happy ones.

The University then proposed that I go abroad to study and come back on a full time basis. I went to Stockholm on the instance of Professor Berglund, where I spent most of my time in diagnosis, although I had some opportunity to observe radiation therapy which, considering the period, was at its peak of perfection at the Radiumhemmet. In spite of the superior character of therapy at this institution, I was not greatly attracted to it and spent almost my entire year abroad in diagnosis, so when I returned to Minneapolis and found Dr. Stenstrom already there, I was not only relieved but happy to have him as a colleague in radiation therapy.

Short wave x-ray radiation had begun to be used for treatment as early as 1899. But the method was still in a rudimentary state because of the relatively poor penetration of the radiation which was then available. In 1914, in Germany, methods of measuring the amounts of radiation were put on a sound basis and finally a 200 kV transformer to produce much more penetrating radiation was manufactured and used successfully for treatment. Radium as well as low voltage Xrays had been used already in the United States with some success. But in the early twenties, machines with a 200 kV capacity were produced by the General Electric Company and I had the opportunity of seeing one of the first of these installed at the Battle Creek Sanitarium for the use of Dr. James Case, in 1924. Interestingly enough, an exactly similar machine was sent to the Roswell Park Memorial Hospital, at that time called the New

*Department of Radiology, University of California, Los Angeles, California.

York State Institute for the Study of Malignant Disease in Buffalo. It was Dr. Stenstrom, then the Physicist at this Institute, who was the first to standardize this type of machine and help to institute it as a unit for the x-ray treatment of patients with cancer.

Dr. Karl Wilhelm Stenstrom was born in Gothenburg, Sweden in 1891, a few years before the discovery of the roentgen rays which were to influence his later life so profoundly. He grew up in Sweden, an intense scholarly student, who developed an interest in Physics in which he received his Ph.D. at the University of Lund. He became a disciple of Professor Siegbahn, one of the distinguished pioneers in the field of radiation physics, and it is not surprising that Stenstrom gained a great knowledge of this subject and especially of its medical aspects. Because of his conscientiousness as a student, he was awarded a Swedish-American Fellowship, which brought him to Harvard University where he had the opportunity to study under the tutelage of William Duane, then Professor of Bio-physics at Harvard, and one of the first pioneers in the study of the physics of radiation. A year later he was called to the New York State Institute for the Study of Malignant Diseases, now Roswell Park Memorial Hospital and, as related above, shortly had the opportunity to standardize one of the first 200 kV x-ray machines in the United States. Professor Holfelder of the University of Frankfurt, later to become the foremost radiation therapist in Germany, was working there with him and Stenstrom was able to acquire a great deal of training in the practical medical radiation therapy of patients. In a few years then, in addition to doing the Bio-physics work at the Institute, he was in fact treating patients, although he was not an M.D. It was a day in which legalities were subordinated to the practicalities of the situation.

It was while living in Buffalo that he met Annette Treble, a young physician in training at the Institute. They were married and formed the sort of partnership which was the envy of their many friends and neighbors and which endured "until death did them part". Annette Stenstrom later studied roentgen diagnosis with me and became an accomplished radiologist in her own right. They had one daughter, Peggy, still living in St. Paul, the wife of Dr. A. M. Richards, and three grandchildren.

His investigations at the New York Institute were many and gave promise of an important research career. Amongst his most significant contributions was the invention of the first unit using radium or radium emanation for treatment at a distance, that is substituting the short penetrating radiation of radium for the high voltage penetrating Xrays which were not yet available.

Radiation therapy at the University of Minnesota Medical School in 1925 was not considered of much importance. It was used only for superficial diseases and then only sparingly. Then, through the wisdom of the Henry Christian family, a great change took place. They gave the University a gift which enabled the establishment of a Cancer Institute, a building erected as a part of the University Hospital but having its own beds and its own radiation unit. One of these new 200 kV machines and 500 mg of radium, largely in the form of emanation, was obtained. Since Dr. Allison had had little experience with this type of radiation and was in fact most reluctant to even undertake the use of what was then considered such a powerful, potentially destructive device—in his own words "I wouldn't touch it with a ten foot pole"—it became evident that someone with experience and training in this area should be obtained. Actually Dr. Stenstrom was brought to Minneapolis from Buffalo originally for the purpose of calibrating the machine and setting up the radiation emanation plant so that both could be used on a practical level. He succeeded so well in his endeavor and made such a profound impression upon Dean E. P. Lyon and on Dr. Arthur Strachauer, who was then Professor and Chief of the Department of Surgery and Chief of the Cancer Institute, that he was asked to remain permanently and take charge of this division. He accepted this assignment, I am sure, with some trepidation; he was entering a field which was presumably for physicians only. No doubt it took a great deal of courage and determination to undertake such an assignment but he had that well-placed confidence in his own ability, which permitted him to take the risks involved. He may have had enough insight to know that, despite the lack of a degree, he had the qualities of the true physician, "the art of caring for the patient, the art of transmitting his knowledge to his students, the great art of making admiring friends of his colleagues". And, in fact, in his clinical work in later years he exhibited a degree of compassion, of meticulous attention to the welfare of the pa-

tient, not always found among physicians. His methods of treatment were relatively conservative, always with the thought in mind that one must not do harm with so potent a weapon. Almost paradoxically then, we find a non-physician who exercised patient care as well as and probably much better than that exhibited by most physicians. Furthermore, in the words of Dr. Juan del Regato, in doing radiation therapy at that time, Stenstrom was "a professional as compared to the many physicians using Xrays who were amateurs in this field."

The Cancer Institute had by far, the first adequate, well equipped radiation therapy program in the Twin Cities and certainly, with the exception of the Mayo Clinic, was the only one of its kind in the state. The idea of a separate Cancer Institute devoted essentially to the study and care of patients with malignancy was not entirely new. The New York State Institute for Malignant Disease was already in existence and there were a few other institutes of this kind in the country. For our part of the United States, it was unique and it was the occasion of considerable controversy. Nevertheless, it was organized and proceeded to develop in an extremely effective fashion. With Dr. Stenstrom in charge, so-called deep x-ray therapy and radium treatments were begun and were attended with a great deal of success.

It is interesting to note that after a number of years, a change in thinking took place and the Cancer Institute eventually lost its identity and became in effect a part of the hospital and of the academic disciplines of the medical school. In time, therefore, Dr. Stenstrom came to be in charge of the radiation therapy using both radium and Xrays. The remaining portions of the institute were induced into surgery. It is instructive to look back on this and consider the fact that the very present time, such Cancer Institutes are being reinstated in many universities throughout the country in the effort to add facilities for the care and study of malignant disease. So that now we have come a full cycle in this regard.

"Stennie," as he was affectionately known by almost all of his friends, students, and colleagues began an academic career of considerable importance. In a short time he and I joined together to form a department of radiology with a graduate training program, residents and a considerable amount of undergraduate teaching. It was a rather extraordinary partnership in many ways. Dr. Stenstrom was essentially a scientist, but inducted by a series of circumstances into a clinical and therapeutic field. I was essentially a clinician, but inducted by a series of circumstances into a scientific and diagnostic field without any real responsibility in therapy. It turned out to be a most excellent arrangement and was one of the first in the country in which it was recognized that therapy and diagnosis might well be separated even though the training of the resident was done jointly. Today, even the training is being separated and the two disciplines have more and more been enjoying an independent status.

For me the knowledge that our residents were getting a sound, yet practical education in Biophysics, far better than in most institutions, was very satisfying. Furthermore our residents were exposed to a scientific, but well oriented clinical experience in radiation therapy in a scholarly academic atmosphere. The virtue of our partnership became apparent almost at once when one of our very first joint graduate students, Dr. Harry Hillstrom, became the first of a long line of residents from the University of Minnesota to become a Chief of a Division or Department of Radiology in the United States. Eventually from this relatively small department there came a host of full time professors of Radiology, at one time comprising some twenty per cent of all the departmental chairmen in this country. Amongst the many outstanding research contributions from Dr. Stenstrom's department, was a new idea about the treatment of Hodgkin's Disease. Dr. Henry Kaplan, who took his diagnostic residency at Minnesota and is now considered one of the foremost authorities on Hodgkin's Disease in the world, notes two papers by Stenstrom and Merner and later by Stenstrom and Nice which influenced his thinking. They may have given the first stimulus for a change in the character of the treatment of Hodgkin's Disease for they showed that a marked increase in the radiation intensity might result in a cure rather than mere palliation.

I can recall discussing this with Dr. Stenstrom and his insistence that it might well be possible to cure Hodgkin's Disease by radiation alone. In one of our first conferences on Radiation Therapy held in the Center for Continuation Study, a number of radiologists from the East entered into a vigorous controversy with Dr. Stenstrom over this

question. They insisted that it was reckless and futile to treat Hodgkin's Disease with excessive doses since there was no possibility of a cure, all one could hope for was palliation. Dr. Stenstrom by this time already had several cases with fairly long standing remissions which almost appeared to be cures. These were cases, which conservative as he was, he had treated much more intensively than was the custom at that time. One such patient was one of our leading citizens, a most important member of the Swedish community. He had a mass in his neck which proved on biopsy to be Hodgkin's. There was no evidence of any other lesions. So here was a local lesion, in a position where intensive treatment could be done without risk of injury. Dr. Stenstrom treated far more vigorously than was the custom at that time and in fact affected what appeared to be a cure.

This was a period in which radiation therapy was developing with great rapidity with many investigators hastily writing paper after paper citing case reports. Many of these investigations were most superficial. Dr. Stenstrom did not respond to this temptation. All of his papers reflect his scholarly, critical, extremely honest scientific attitude. In addition to one of the first didactic manuals on radiation therapy for physicians, he published over a hundred scientific papers, all of which carried with them a considerable degree of importance in the development of radiation therapy.

His publications show a great versatility ranging over a broad spectrum of scientific activity in this field. They include studies on the effects of radiation on certain chemical compounds, on tissue cultures of lymph nodes, and on the effects of radiation on mineral oil droplets. There are studies of the physical and biological characteristics of radium, Xrays, ultra-violet rays, and diathermy and there are investigations of methods of measurement and protection against radiation, on instrumentation and on the standardization of radium. And finally, there are many papers on the effects of radiation on patients with a great variety of diseases with special attention to carcinoma of the cervix, Hodgkin's Disease, and carcinoma of the ovary.

Later in his career he obtained better and more powerful equipment for producing penetrating radiation. Finally he was one of the very first therapists in the United States to utilize radioactive Cobalt for treatment, a method which later became very popular.

As time went on, he became interested in the applications of ultra-violet therapy and other types of physio-therapy, especially investigating the mechanisms of the effects of diathermy. There was no organized program of physical medicine at the University at that time, so that it was only natural that he should assume this responsibility. Eventually, of course, various physicians assumed leadership in Physical Medicine on a full time basis and he was able to turn his attention to other matters, notably nuclear medicine. A great interest in the use of isotopes, both for research and for treatment was then developing. Only radioactive iodine and some phosphorus were being used but it was important that they be measured properly and that safeguards for both the physician and the patient be established. That responsibility he also assumed. In time this small beginning developed into a very comprehensive division of the Department of Radiology, now recognized as one of the most productive and important scholarly enterprises of the medical school headed by Dr. Merle Loken, who was one of Dr. Stenstrom's students.

Since Stenstrom was not a doctor of medicine, we found it necessary, largely from a medico-legal standpoint, for him to have an associate physician, one of our residents who had completed his training and could continue on a full time basis in the division. Dr. Cyrus Hansen became the first of many such associates in radiation therapy. He was followed by a succession of individuals, many of whom have since attained important positions both in hospitals and in private practice. One of our residents, who came from Norway on a Scandinavian-American Fellowship, Dr. Halvor Vermund, was greatly influenced by his work with Dr. Stenstrom. He is presently Chief of the Division of Radiation Therapy at the University of California at Irvine. Another, Dr. Donn Mosser, succeeded Dr. Stenstrom on his retirement. It can well be said of Dr. Stenstrom that he had to fight for his place in the medical school hierarchy, but like the proverbial ant, "He found kingdoms in a foot of ground".

In 1948, his contributions, both as a scientist and as a citizen were recognized when he was awarded the Order of the North Star by the Swedish Crown. In 1958 he received the American Cancer Society Award for distinguished service in the control of cancer.

Wilhelm Stenstrom was first of all a gentleman

in the best sense of the word. His more notable characteristics were his meticulous methods, his critical sense, his unfailing honesty and his devotion to his specialty. He was at once dignified and modest; he could listen and adapt but could also be stubborn in defense of his ideals and his position. He had a quiet dry humor which enlivened his discussions. It can truly be said of him in the words of Osler, "He bore success with humility, the affection of his friends with pride."

After thirty years in the department, there came a time to listen to the kind voices of friends and to consider that the race was over even though the work is never done. He felt it would be best to pass on his work to younger hands so he retired to live quietly and productively with his beloved wife in a new home on Anna Marie Island in Florida. There he took a great interest in construction, in the theater and the various activities in the small community where he and Dr. Annette Stenstrom became important figures. Their conduct of their remaining years was ideal, one that many of us could look to as an example. He did come back to visit Minneapolis from time to time to greet old friends, to see the progress in the Division of Radiation Therapy, which continued to expand, to elaborate on the firm foundation which he had created. Finally he passed away at his home very quietly after a very brief illness on November 7, 1973 at the age of 82.

In his honor and as a tribute to his great contributions to the medical school, his students and friends have set up a lectureship which we hope will continue throughout the years. Contributions by distinguished radiation therapists we hope will add to our knowledge in the future. All of us mourn his passing but feel that his contributions were so substantial, the impact of his personality so appealing that he accomplished all anyone could desire in the brief span of life that we have on this earth.

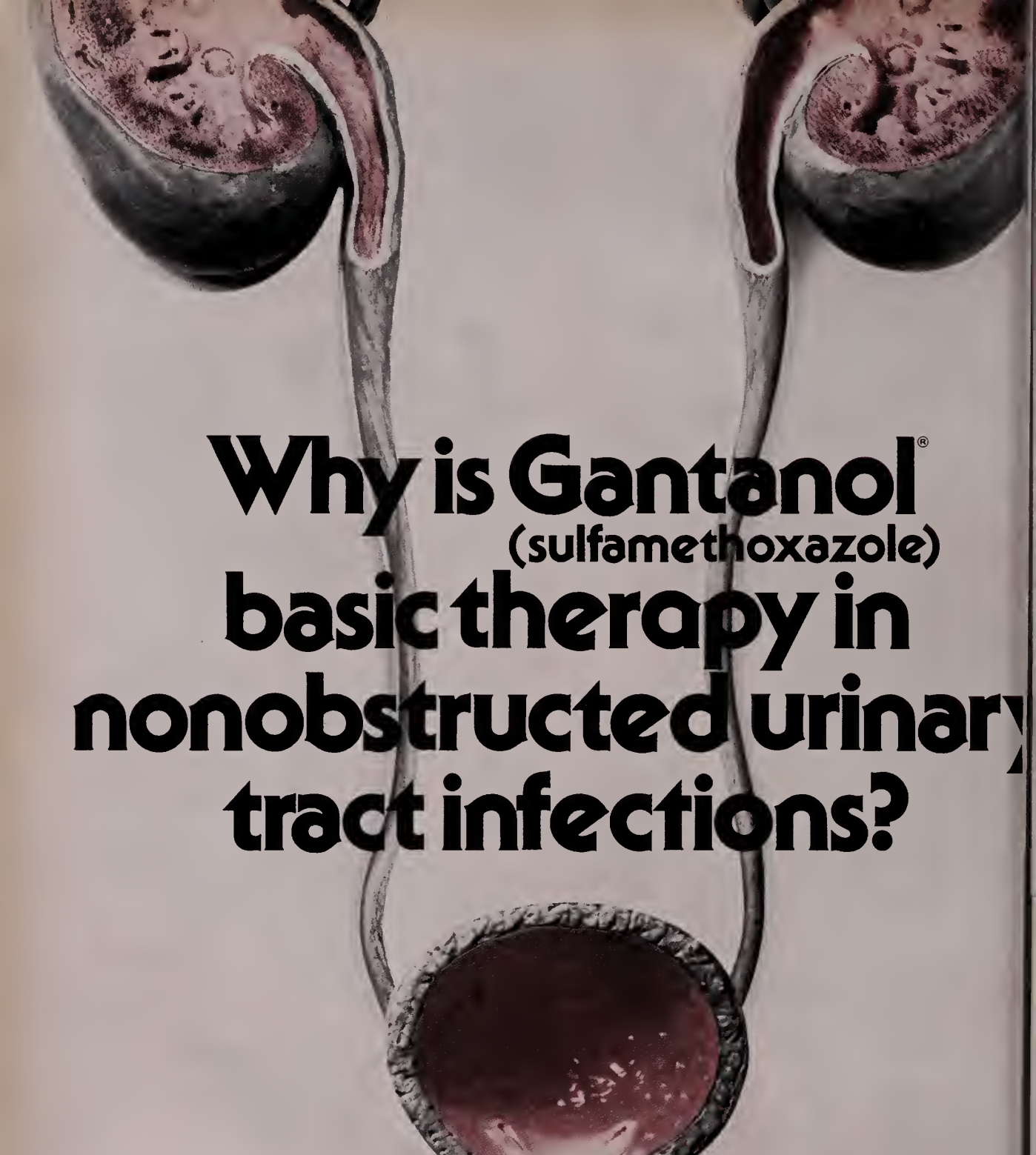
Request for Physician's Art Work

For many years the Board of Editors of MINNESOTA MEDICINE has recognized and supported photographic and other artistic talents of the members of the Minnesota State Medical Association publishing cover pictures in color of their work. Our series of color covers have received much favorable comment and many journals have followed us in the use of color art in this manner.

We solicit color photographs including pictures of all art forms created by members of the association. These must be technically excellent to show off the subject to its best advantage.

Although in the past we have printed cover pictures depicting many distant parts of the world, photographs of life in Minnesota will be given preference. Pictures will be returned if identified with the name and address of the physician. Please submit your picture as prospective cover subjects to the Editor of MINNESOTA MEDICINE, 375 Jackson St., St. Paul, Minnesota 55101.

Farrell Stiegler, M.D.
Cover Editor



Why is Gantanol® (sulfamethoxazole) basic therapy in nonobstructed urinary tract infections?

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Indications: Acute, recurrent or chronic nonobstructed urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms. **Note: Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response; add aminobenzoic acid to follow-up culture media. The increasing frequency of resistant organisms limits the usefulness of antibacterials including sulfonamides, especially in chronic or recurrent urinary tract infections.** Measure sulfonamide blood levels as variations may occur; 20 mg/100 ml should be maximum total level.

Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate c vent sequelae (rheumatic fever, glomerulonep of such infections. Deaths from hypersensitivity tions, agranulocytosis, aplastic anemia and other dyscrasias have been reported and early clinical signs throat, fever, pallor, purpura or jaundice) may indicate s blood disorders. Frequent CBC and urinalysis with micro examination are recommended during sulfonamide therapy. I cient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired re hepatic function, severe allergy, bronchial asthma; in gluc phosphate dehydrogenase-deficient individuals in whom related hemolysis may occur. Maintain adequate fluid int prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, tic anemia, thrombocytopenia, leukopenia, hemolytic anemia

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hypoprothrombinemia and methemoglobinemia); *allergic ns* (erythema multiforme, skin eruptions, epidermal necrolyticaria, serum sickness, pruritus, exfoliative dermatitis, anatoid reactions, periorbital edema, conjunctival and scleral on, photosensitization, arthralgia and allergic myocarditis); *intestinal reactions* (nausea, emesis, abdominal pains, hepaiarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* ache, peripheral neuritis, mental depression, convulsions, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous ns* (drug fever, chills, toxic nephrosis with oliguria and , periarteritis nodosa and L.E. phenomenon). Due to certain cal similarities with some goitrogens, diuretics (acetazolathiazides) and oral hypoglycemic agents, sulfonamides have d rare instances of goiter production, diuresis and hypoglyas well as thyroid malignancies in rats following long-term istration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

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Warnings: Not for use in children under three years of age. Should not be administered repeatedly to patients with pulmonary, cardiac, renal, or hepatic disease.

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Dosage and Administration: Children 3 to 6 years age: One 2 gr suppository rectally 3 or 4 times dai not to exceed 8 grains per day.

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*Trademark Union Carbide.

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APPLY ENZYME
Apply a layer of TRAVASE Ointment. Assure intimate contact with necrotic tissue and complete wound coverage.

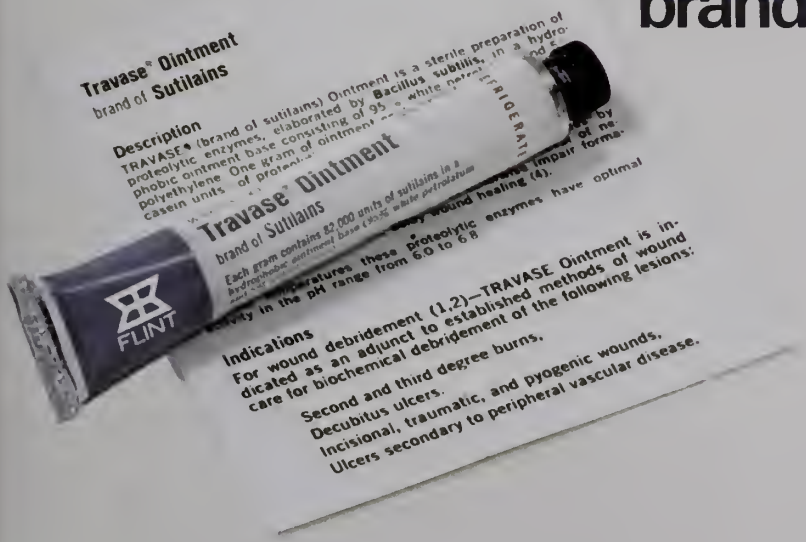


APPLY MOIST DRESSING
Apply loose moist dressings (most important with dry leathery eschar).



CHANGE DRESSINGS
When changing dressing, gently wipe away the dissolved material. Repeat the procedure, including application of TRAVASE Ointment, 3 to 4 times per day for best results.

Travase® Ointment
brand of Sutilains



FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC
Deerfield, Illinois 60015

Please see next page for prescribing information.

Travase® Ointment brand of Sutilains

ulcers

TERRY V. CARLE, M.D., CLINICAL INSTRUCTOR, DEPT. OF PHYS. MED. & REHAB., CRAIG REHABILITATION HOSPITAL, UNIVERSITY OF COLORADO



Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



After nine days of TRAVASE therapy, debridement is nearly complete and granulation evident.

burns

DALE B. DUBIN, M.D., DIPLOMATE, AMERICAN BOARD OF PLASTIC SURGERY, TAMPA, FLORIDA



Before treatment . . .



48 hours following treatment with TRAVASE Ointment on right hand; left hand is control.

Travase® Ointment

(brand of Sutilains)

Indications: For wound debridement, TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

- Second and third degree burns,
- Decubitus ulcers,
- Incisional, traumatic, and pyogenic wounds,
- Ulcers secondary to peripheral vascular disease.

Contraindications: Application of TRAVASE Ointment is contraindicated in the following conditions:

- Wounds communicating with major body cavities,
- Wounds containing exposed major nerves or nervous tissue,
- Fungating neoplastic ulcers,
- Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE upon the developing fetus.

Warning: Do not permit TRAVASE Ointment to come into contact with the eyes. If contact is made, immediately rinse with copious amounts of water, preferably sterile.

Precautions: A moist environment is essential to optimal activity of the enzyme. Enzyme activity may also be impaired by certain agents (see package insert). Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

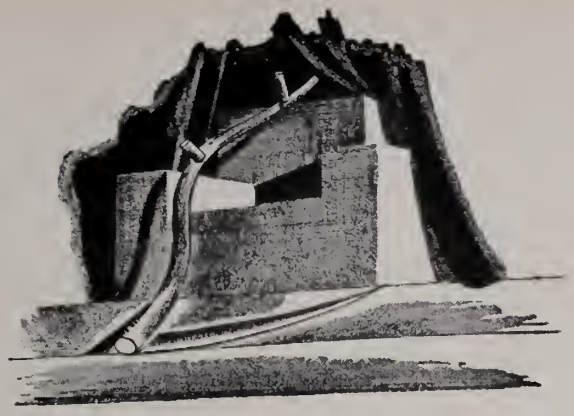
Adverse Reactions: Consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

DOSAGE AND ADMINISTRATION: STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECTIVE RESULTS OF TREATMENT:

1. Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., hexachlorophene, silver nitrate, benzalkonium chloride, nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g. sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

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Deerfield, Illinois 60015



In Memoriam

FRANK S. McKINNEY, M.D.

Dr. Frank S. McKinney, 88, Minneapolis surgeon, died November 1. Born in Chapin, Illinois, Dr. McKinney obtained his medical degree from Northwestern Medical School. He interned at Wesley Hospital in Chicago and did postgraduate work at the Vienna University in Vienna.

He was a member of the American Medical Association and Hennepin County Medical Society and a Life and 50 Club Member of the Minnesota State Medical Association.

Dr. McKinney is survived by his daughter, Kathryn.

MURLY A. BORGERSON, M.D.

Dr. Murly A. Borgerson, 71, Hanley Falls physician, died August 28. He was a graduate of the University of Minnesota Medical School.

Dr. Borgerson was a member of the American Medical Association, the Camp Release District Medical Society and the Minnesota Medical Association.

He is survived by his wife, Emma.

JAMES J. KOLARS, M.D.

Dr. James Kolars, 74, longtime Faribault physician and surgeon, died October 17. Born in Montgomery, Dr. Kolars took his pre-medical school degree from the University of Minnesota and graduated from Creighton University Medical School in Omaha.

He was a member of the American Medical Association and the Rice County Medical Society and a Life Member of the Minnesota State Medical Association and the AMA of Vienna.

Dr. Kolars is survived by his wife, Irene, one son, Dr. James Kolars, Jr. of Fargo, three daughters, Kathleen, Terry and Sharon.

ROBERT V. SCHUMACHER, M.D.

Dr. Robert Schumacher, 36, Minneapolis physician, died November 24. He had obtained his medical degree from the University of Wisconsin in Madison.

Dr. Schumacher was a member of the American Medical Association and the Hennepin County Medical Society and a Residency Member of the Minnesota State Medical Association.

He is survived by his wife, Sandra, daughter, Bethney, and sons, John, Clark and Michael.

MOSES BARRON, M.D.

Dr. Moses Barron, 91, whose research helped in the discovery of insulin, died December 22. He had been on the University of Minnesota Medical School faculty for 40 years as a teacher of clinical medicine.

A scientific paper Dr. Barron wrote in the early 1920s provided the key for the discovery of insulin by Dr. Frederick Banting, a Canadian, who won the Nobel Prize. He was the first chief of staff at Mount Sinai Hospital in Minneapolis and a prime mover in the development of the institution.

Dr. Barron was a member of many scientific and medical organizations in Minnesota and the nation. He headed the Hennepin County Medical Society in 1931 and 1932.

He is survived by three sons, Louis, Dr. David of Skokie and Dr. Jesse of St. Louis Park and a daughter, Mrs. Charles Stein.

JAMES WOLLARD BRATHOLDT, M.D.

Dr. James W. Bratholdt, 62, Watertown physician, died November 25. He had practiced in Watertown since 1941. His medical education was obtained at the University of Minnesota Medical School.

Dr. Bratholdt was a member of the American Medical Association, the Minnesota Medical Foundation, the Minnesota State Medical Association, Scott-Carver County Medical Society, Minnesota Academy of General Practice and was instrumental in working for the establishment of the Watertown Community Hospital.

He is survived by his wife, Norma, two sons, Michael and James, and two daughters, Jennifer and Shelley.

JOHN H. GLAESER, M.D.

Dr. John Glaeser, 53, otolaryngologist, died December 11. He was on the staffs of North Memorial, Fairview Southdale and University of Minnesota Hospitals and had attended the University of Minnesota Medical School.

Dr. Glaeser was a member of the Hennepin County Medical Society, the American Medical Association and the Minnesota State Medical Association.

He is survived by a son, Tom, and two daughters, Joan and Janet.

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Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

BUILDING NEW CLINIC IN BROOKLYN PARK—A Minneapolis suburb of 30,000 population. *This 12 to 15 physician clinic is scheduled for occupancy in July 1975. *We solicit the physicans input regarding his space layout and decorating scheme prior to construction. *This facility will be of the highest quality at the lowest possible sq. ft. cost. For leasing or other information contact: Rick Brendsel or Dick Mueller, Real Estate 10, Inc. Commercial-Investment Division, 7420 Unity Avenue North, Minneapolis, Minnesota 55443. (612) 566-6028.

OCEAN FRONT APARTMENTS—2 Florida physicians will rent luxury ocean front condominium apartments—Daytona area. 2 BR, 2 bath, pool, sauna, tennis, golf nearby. Disney World 1 hour via Interstate. Excellent for summer family vacation also. 904-373-7064 or 904-372-5467—evenings.

WANTED—LOCUM TENENS to the summer of 1975, at Hibbing, Minnesota, license required, call K. E. Ahola, M.D., area 218-262-3441.

RIVERS EDGE MEDICAL CLINIC—Farmington, Mn. needs two additional General Practitioners to practice in a nearly new Clinic, Hospital and Nursing Home. Fast growing area just 45 minutes from St. Paul-Minneapolis. Metropolitan advantage with Community living. Contact M. H. Hunter, M.D. (612) 463-7181.

LOCUM TENENS AVAILABLE—most evenings, nights, weekends or for vacations. Have a car, can help almost anywhere in Minnesota. Have license, can handle any type of emergency; years of experience. Call RAU at 1-612-425-6056 or write. Box 22008, Robbinsdale, Mn. 55422.

EXPANDING TEN MAN FAMILY PRACTICE GROUP in southern Minnesota. Seeks GENERAL PRACTITIONER OR INTERNIST for summer of 75. New clinic adjacent to a new 114 bed hospital. Fairmont is a progressive community (City of Five Lakes). Starting salary open, early partnership opportunity. Contact D. E. Grandgenett, Fairmont Medical Clinic. 507-238-4263.

IMMEDIATE OPENINGS for Family Practitioner and Internist; community of 5000; 50 miles west of Minneapolis; 8 Doctors on 54 Bed Hospital Staff rotating night and weekend coverage. Salary negotiable; independent or associate practice. Contact Hospital Admin., David Larson, 705 W. 18th Street, Glencoe, MN 55336 or phone (612) 864-3121 collect.

WANTED—Internists and Family Practitioners to join congenial five man group in central Wisconsin. Completion of new office complex adjoining new modern hospital expected soon. Excellent starting salary with liberal time off for vacation, postgraduate studies, etc. Contact Clifford Starr, M.D., Riverwood Clinic, 1011 3rd Street South, Wisconsin Rapids, Wisconsin, (715) 423-1300 or Dean Nelson, Administrator, Riverview Hospital, 410 Dewey Street, Wisconsin Rapids, Wisconsin, (715) 423-6060.

WAYZATA MEDICAL BUILDING OFFICE SUITES—Located in the fastest growing suburban area in the Twin Cities. We offer:

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WANTED—A great middle sized city only fifty minutes from the Twin Cities can offer instant success for the G.P. and Internist who would like a liberal call schedule, excellent hospital and eight congenial partners. A collect call or write to Arlene Pfeffer, Business Manager, Faribault Clinic, Ltd., 924 N.E. First Street, Faribault, Minnesota 55021, phone: 507-334-2921.

DOCTORS . . . RURAL MINNESOTA/WISCONSIN NEEDS YOU. (All Specialties)—A professional and time-saving approach to practice relocation. Enjoy the best of either world. Over 50 choice opportunities to choose from at no cost to you. For discrete and confidential assistance in helping you find the proper "niche" for you and your family. Call (612) 436-5161 collect. Midwest Medical, Inc., Lakeland, Minnesota 55043.

STAFF PHYSICIAN—Mankato State College is seeking a staff physician capable of general medicine and committed to working with young adults. Located in south central Minnesota the College has an on-campus enrollment of 9,500 students, and is situated in a metropolitan area of 50,000. Attractive five day work week, vacation when school not in session, position available July 1, 1975. Contact: Karen Delesha, Director, Student Health Service, Mankato State College, Mankato, Minn. 56001. Phone (507) 389-2726.

INTERNIST, UROLOGIST ANESTHESIOLOGIST —to join progressive group serving central Minnesota lake country. Modern clinic and 150 bed hospital. $40,000 first year, then partnership. Good schools, clean, uncrowded environment, lakes nearby. Contact Dr. George M. Fortier, 612-632-5305 or 612-632-3611, Little Falls Clinic, Ltd., Little Falls, Minnesota.

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FAMILY PHYSICIAN SEEKS PRACTICE in small rural Minnesota community with hospital. 28 years old, board eligible, residency trained, presently in US Navy, available July 1976. Resume sent on request. S. J. Carlson MD, 305 Woodhaven, Havelock, N.C. 28532.

18 MAN MULTISPECIALTY clinic in scenic Coulee region of Western Wisconsin seeks general pediatrician preferably with subspecialty training in allergy. Contact: William A. Blank, M.D., La Crosse Clinic Ltd., 212 South 11th Street, La Crosse, Wisconsin 54601.

PEAVEY PARK MEDICAL CLINIC—For sale, or lease. Completely equipped, 3400+ ft.—examining rooms, plumbing, labs, spacious reception area, private consulting offices, security system, muzak. Ample patient and staff parking. $5000+ rental property income from 4 unit, attached residential apartment. Terms. For price details and additional information, call Mike Hoffman, 612/933-7700. Stan Barton & Assoc's., 8800 W. Hwy 7, Mpls., Mn 55426.

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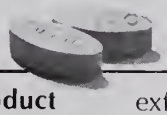
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Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

A high assurance of clinical efficacy

- in cystitis, pyelonephritis and pyelitis diagnosed as chronic
- against susceptible strains of the common urinary tract pathogens, usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species.



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species).

Note: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in chronic and recurrent urinary tract infections.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia in elderly patients on diuretics, primarily thiazides. Sore throat, fever, pallor or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if significantly reduced count of any formed blood element is noted. Data are insufficient to recommend use in infants and children under 12.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, allergy or bronchial asthma; and in those with glucose-6-phosphate dehydrogenase deficiency, where hemolysis may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12.

Usual adult dosage: Two tablets b.i.d. for 10 to 14 days. For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
Above 30	Usual standard regimen
15-30	2 tablets every 24 hours
Below 15	Use not recommended

Supplied: Tablets, each containing 80 mg trimethoprim and 400 mg sulfamethoxazole—bottles of 100 and 500; Tel-E-Dose® packages of 1000; Prescription Paks of 40, available singly and in trays of 10.

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Division of Hoffmann-La Roche Inc.
Nutley, New Jersey 07110

Bactrim™

Each tablet contains 80 mg trimethoprim and 400 mg sulfamethoxazole.

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A high assurance of antibacterial activity
in cystitis, pyelonephritis and pyelitis diagnosed as chronic and due to susceptible organisms.

Before prescribing, please consult complete product information, a summary of which appears on preceding page.

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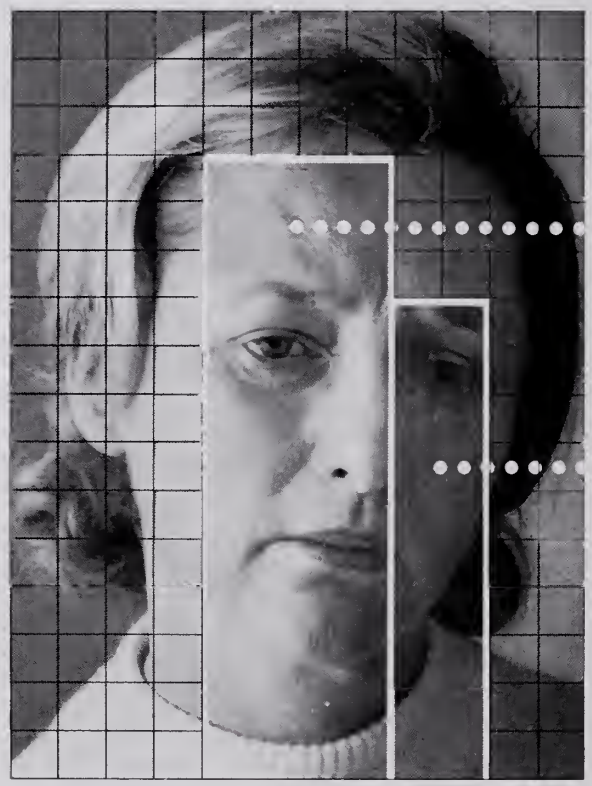


"... Forest"

Robert O. Fisch, M.D.

MARCH 1975

Both often



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in fr and/or severity of grand mal seizu require increased dosage of stand convulsant medication; abrupt with may be associated with temporary crease in frequency and/or severi seizures. Advise against simultaneu gestion of alcohol and other CNS d sants. Withdrawal symptoms (sim those with barbiturates and alcoh occurred following abrupt discont (convulsions, tremor, abdominal cle cramps, vomiting and sweatin addiction-prone individuals under

respond to one

According to her major
ptoms, she is a psychoneu-
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ngs, part of the problem
sound like depression.
is because her problem,
ough primarily one of ex-
ive anxiety, is often accom-
ed by depressive symptom-
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provide relief for both—as
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s associated with it are also
relieved.
There are other advan-
s in using Valium for the
agement of psychoneu-
anxiety with secondary
essive symptoms: the
hotherapeutic effect of
um is pronounced and
d. This means that im-
ement is usually apparent
in the patient within a few days rather than in a week or two, although it may take longer in some patients. In addition, Valium (diazepam) is generally well tolerated; as with most CNS-acting agents, caution patients against hazardous occupations requiring complete mental alertness.

Also, because the psychoneurotic patient's symptoms are often intensified at bedtime, Valium can offer an additional benefit. An *h.s.* dose added to the *b.i.d.* or *t.i.d.* treatment regimen can relieve the excessive anxiety and associated depressive symptoms and thus encourage a more restful night's sleep.



Valium® (diazepam)

2-mg, 5-mg, 10-mg tablets

in psychoneurotic
anxiety states
with associated
depressive symptoms

eillance because of their predisposi-
to habituation and dependence. In
nancy, lactation or women of child-
ing age, weigh potential benefit
nst possible hazard.

autions: If combined with other psy-
ropics or anticonvulsants, consider
fully pharmacology of agents em-
ed; drugs such as phenothiazines,
otics, barbiturates, MAO inhibitors
other antidepressants may potentiate
ction. Usual precautions indicated in
nts severely depressed, or with latent
ession, or with suicidal tendencies.
Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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The patient with gastritis:

another type for TYLENOL® analgesic table



When the gastritis patient has condition requiring an analgesic, a n problem arises. Aspirin's irritating effect on the gastric mucosa is well documented.[1,3]

TYLENOL analgesic tablets, the other hand, are unlikely to cause local irritation,[2,3] which is why they a preferred in the patient subject to gastritis.

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Supplied: Tablets, 325 mg.
For Children:
Elixir, 120 mg./5cc. (alcohol 7%).
Drops, 60 mg./0.6cc. (alcohol 7%).
Chewable Tablets, 120 mg.

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Safer than aspirin, yet just as effective f relief of pain and feve

TYLENO

acetaminophen tablet

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President's Letter

Medical Liability - Medicine's Challenge

ALTHOUGH THE WORDS "crisis" and "emergency" seem to be overused lately, they do describe the problems in the medical liability insurance field. The number of claims has reached an all time high and is still rising. St. Paul Companies report that of the doctors they insure, one out of ten has a claim pending. The situation has become intolerable. Premiums have climbed to an astronomical height; even these are inadequate, and insurance companies are dropping out of the field or asking for even larger rate increases. They report losses from this portion of their business.

What has caused this flood of litigation? Without question, much of it is due to changes occurring in society. The age of accountability and the rise of consumerism play a part. There is no question that the impersonal relationship between some practitioners and their patients has made litigation more frequent; it is difficult to bring action against a friend and confidant. Unreasonable expectations are common among many patients; this has been termed the "Dr. Welby" or "Medical Center" syndrome. The physician, as everyone else, is not infallible and medical judgments are not easy, except in retrospect. Also, lay publication of scientific advances fail to clarify that results in the world of biology and physiology do not always follow predictable patterns in the medical world. These same advances, with more sophisticated diagnostic and surgical procedures, have increased the physician's exposure to unavoidable, untoward results. The advent of no fault insurance reportedly has decreased personal injury liability claims and increased medical liability claims.

Some of the reasons for the increasing number of claims directly involve the physician, so each of us must give more consideration to improving our relationship with our patients. Words of explanation concerning expected results and possible risks will do much to dispel unreasonable expectations. We can no longer use the optimistic, "You will be as good as new" or "You will be better than ever." We must be realistic in our appraisal of results.

Many formal solutions are also being suggested. Some, such as no fault medical liability insurance, voluntary arbitration, and patient compensation commissions would only increase the problem. Others would make us dependent on the federal government for liability insurance, and would in the end limit our freedom. Of the proposed solutions only compulsory arbitration seems to have any chance of giving relief. Its primary benefit would be in speeding settlement of claims and reducing cost of defense and size of awards.

The Minnesota State Medical Association has appointed an ad hoc committee to meet with representatives of the Minnesota Hospital Association and insurers to explore this avenue. Under arbitration, the number of claims would unquestionably increase. Anyone who does not achieve the results he expected would have redress to arbitration. One can only imagine the time physicians would spend in arbitration hearings. Compulsory arbitration is an untried method with uncertain effects, but it seems worth exploring.

The present court system has the advantage over proposed alternatives because of its long established rules of procedure and evidence. One of the problems is that these rules have recently been relaxed through Supreme Court decisions. The State Medical Association hopes that through legislative action there can be a tightening of the rules of evidence and procedure. Much effort is being put into this approach, and bills to accomplish it will soon be introduced to the Legislature. When the time is appropriate, physicians will be called upon to contact and explain these matters to their elected representatives. This is a call you must not ignore. Wide physician participation is essential if anything is to be accomplished. Minnesota is still in a relatively favorable position in comparison with other states, but the situation is explosive and can change quickly.

None of us would wish to deny compensation to those who are injured through negligent or incompetent treatment, but through individual discussion with patients we must reduce nuisance claims brought by dissatisfied or irate patients. Through concerted effort, we must explain our recommendations to the law makers and the public. We must offer treatment for this medical emergency.

Bernard Hall M.D.

President
Minnesota State Medical Association

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Editor's Notebook

MINNESOTA MEDICINE and minny

What makes a good medical journal?

Franz J. Ingelfinger, Editor of the *New England Journal of Medicine,* lists these ingredients: wisely selected topics, carefully evaluated reports, fastidious editing, dependable publishing schedule, and personality of the Editor.[1] Doctor Ingelfinger says a dash of humanity also helps.

To these ingredients I would add variety and humor.

Variety

Variety is the lifeblood of a general journal like MINNESOTA MEDICINE. After all, our readers are a variegated lot. So our policy will be to vary our articles so each issue will have at least one article that interests you. As the Editor of the *British Medical Journal* once said of the contents of that journal: ". . . something for everybody, not everything for somebody."[2]

Humor

Humor is a fragile and elusive thing. I shall not try to describe here its use in medical writing—though I have had a go at that before.[3] But in whatever fashion you use humor, it is a quality that keeps a journal alive, read, and readable. You may have noticed our discriminating Cover Editor, Farrell Stiegler, introduced a touch of humor on the cover of the January issue, "Snowshoeing," by selecting the photograph of an exhausted physician's wife for the monthly subject. From time to time you may see other fun creep in.

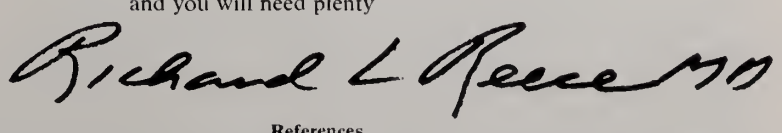
minny

Speaking of creeping, I would like to introduce another feature: a mascot for MINNESOTA MEDICINE. A mascot? Yes, a mascot. But why? Because I have one in mind, that's why. His name is minny. He is a literary cockroach who composes free verse by hurling himself head downward against the typewriter keys. He is not heavy enough to lock the shift key, so when he writes you will not see any capitals, apostrophes, or quotation marks. It's just as well. Mundane tasks like punctuation keep his spirit from soaring. Despite his high spirits, minny still looks at life from the underside, insect fashion. Physical limitations do not dampen his style: minny is bold, disrespectful, fun-loving, contemptuous of detail, and hungry for the literary life.

minny traces his lineage to archy, a cockroach created by Don Marquis (1876-1937), a columnist for the *New York Sun;* and to barney, who held forth as insect laureate for the *St. Barnabas Medical Staff Bulletin* in Minneapolis from 1966 to 1970. Both those publications are now defunct, but the literary spirit of archy and barney, transmigrated from the soul of William Shakespeare, lives on in minny.

I must warn you minny is independent. Expression is the need of his soul, and liberty is the name of his game. His poems, as you are about to see, are irreverent.

mr minnesota medicine editor
i accept the position
because mascots bring luck
and you will need plenty



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Amylase Production by Bronchogenic Small Cell Carcinoma

SEYMOUR HANDLER, M.D.*

Massive production of the exocrine hormone amylase in a case of metastatic bronchogenic small cell carcinoma is described. Amylase production by the tumor was proved by persistence of high levels in serum and urine for many months and by tumor assay of autopsy. Other sources of amylase were excluded.

ENDOCRINE SYNDROMES due to non-endocrine neoplasms have been increasingly described[1-9] in the past fifteen years. Most of the malignant tumors have been bronchogenic small cell or oat cell carcinomas but also included have been epithelial thymomas, islet cell pancreatic carcinoma, medullary thyroid carcinoma, bronchial and gastric carcinoids, and several other less common tumors. The endocrine syndromes include ACTH production with Cushing's syndrome, hypercalcemia, inappropriate secretion of antidiuretic hormone, myasthenia, carcinoid syndrome (production of 5-hydroxytryptophane), and others.

All of the endocrine syndromes are produced by endocrine-acting substances with systemic effects. A very few cases of production of an exocrine enzyme by a bronchogenic carcinoma have been described.[10-12] The most recent contribution by Ammann and Berk[12] documents two cases of amylase production causing persistent hyperamylasemia. One of these cases examined at postmortem examination had high amylase activity in tumor tissue. To add to the very small literature available on the subject, and to demonstrate the possible occurrence of clinical confusion, a case from our experience is offered.

Case Report

The patient is a 39-year-old white female admitted to the hospital in April, 1972 with upper abdominal pain of several days duration. The pain had not responded to conservative measures. The past medical history was unremarkable. She drank only a small amount of alcoholic beverages but was a heavy cigarette smoker. She was obese, but her abdomen was negative and she did not appear acutely ill.

The hemoglobin on admission was 13.5 gm/dl, WBC 11,500 with a normal differential, and the urinalysis was negative. The serum chemistry survey indicated LDH 450 units (normal up to 120), alkaline phosphatase 21 King-Armstrong units (normal KAU up to 17) and SGOT 54 units. The serum amylase was 2400 Somogyi units/dl (normal up to 200 SU) and the urine amylase was 1500 SU/hr (normal up to 250). Chest x-ray indicated a density in the left upper lobe. Oral cholecystogram, barium enema and upper gastrointestinal x-rays were negative.

Despite the absence of abdominal physical findings, the elevated urinary and serum amylase prompted a clinical diagnosis of acute pancreatitis. She was treated with nasogastric suction, anticholinergic drugs, intravenous fluids and parenteral antibiotics. The abdominal distress relented but repeated measurements of urine and serum amylase (Figure 1) revealed values ranging from 10-15 times the upper limit of normal. After three weeks of hospitalization, examination suggested either an enlarged liver or a mass possibly representing a pancreatic pseudocyst. A radioactive liver scan revealed perfusion defects consistent with multiple metastases. Laparotomy revealed a normal pancreas, gallbladder and common bile duct. Multiple tumors were noted in the enlarged

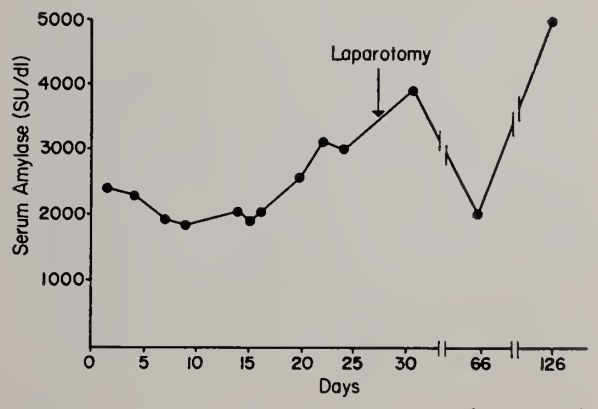


Fig. 1—Serum amylase values over a four month clinical course.

*Assistant Professor, Department of Laboratory Medicine and Pathology, University of Minnesota and Pathologist, North Memorial Medical Center, Minneapolis, Minnesota.

liver and biopsy revealed metastatic small cell carcinoma (Figure 2), consistent with a primary bronchogenic tumor. The patient was discharged a few days later.

The patient was readmitted in two weeks with chronic weight loss and progressive deterioration. She had increased cough and the serum alkaline phosphatase was further elevated.

On June 9 the serum amylase was 2500 units (Figure 1). The patient was treated with cyclophosphamide and discharged to a nursing home. She further deteriorated and came in for the terminal admission in August, 1972. Serum amylase on August 4 was 4800 SU/dl and the urine amylase was 1170 SU/hr. She expired on the third hospital day.

Postmortem examination revealed a tumor in the left upper lobe bronchus, completely obstructing the lumen, creating a mass extending into the pulmonary parenchyma measuring 2.5 × 2.2 cm. The liver was massively enlarged and replaced by multiple metastases from 1 to 12 cm in diameter. The gallbladder, common bile duct and pancreas were normal. Metastases were found in the ovaries, retroperitoneal lymph nodes and bone marrow.

Selected fresh tissues from the autopsy were assayed for amylase activity by the amyloclastic method of Rice.[13] This method was used for the urine and serum amylase determinations. The tissue was homogenized and extracted with saline. Two separate liver metastases had 128,000 and 101,000 Somogyi units/gm of wet tissue each respectively. A portion of the bronchogenic carcinoma had 80,000 Somogyi units/gm of wet tissue. Liver tissue not grossly involved with tumor had almost no detectable amylase activity.

Discussion

Evidence to support the conclusion that the bronchogenic carcinoma was the source of the amylase necessarily excludes all other etiologies[14-16] of prolonged hyperamylasemia. Most causes of hyperamylasemia are diseases of the pancreas, gallbladder, and bile ducts. Also included are acute sialadenitis, acute abdominal surgical problems, renal insufficiency, shock and trauma, ruptured ectopic tubal pregnancy and opiate injections. The latter group is excluded by the clinical inconsistency of the entities and because the hyperamylasemia endured for five months. The highest levels of serum and urine amylase occur with inflammatory or obstructive disorders of the common bile duct and pancreas. Hyperamylasemia of over three weeks duration occurred in only six of 233 cases in the review by Veith,[17] and five of the six had a pancreatic pseudocyst. The case of acute pancreatitis reported by Grossman[18] had hyperamylasemia for 165 days but several of the measurements were only slightly above the normal range; the present case had levels 10-20 times the upper limit of normal for a period of five months, most of which time the patient had no abdominal symptoms. The absence of any evidence of pancreatic or biliary disease in the patient's course, laparotomy and autopsy supports the conclusion that the amylase came from the tumor and not from the biliary tree or pancreas.

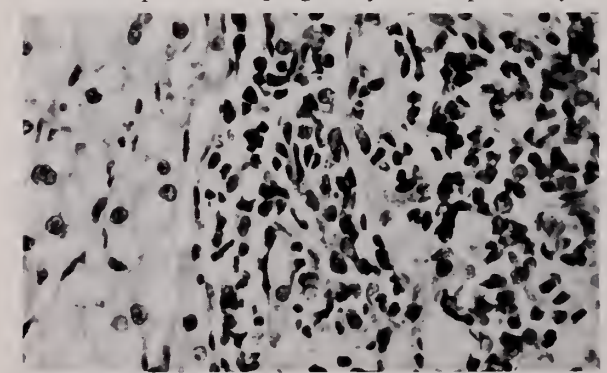


Fig. 2—Photomicrograph (× 400) of liver biopsy with metastatic small cell carcinoma. Normal liver cells at left are contrasted with small dark tumor cells almost devoid of cytoplasm.

Another cause of prolonged hyperamylasemia is macroamylasemia,[19] in which amylase is bound to a serum globulin. The protein binding decreases glomerular filtration of amylase, thereby reducing renal excretion and causing high serum levels. Macroamylasemia can be excluded in the present case because the urine amylase levels were always elevated. Extrapolating from several of the urinary amylase values in the present case, 24 hour excretion would total between 250,000 and 400,000 Somogyi units. These values compare favorably to the 24 hour excretion of 137,000 units in Berk's[12] case, 150,000 units in Weiss'[10] case, and the average normal urinary excretion of 2,000 units/day.

The final evidence of the neoplastic origin of the prolonged hyperamylasemia is the assay of the tumor obtained at autopsy. Both the primary bronchogenic tumor and liver metastases had high levels of amylase activity, whereas liver tissue not involved with metastatic tumor had virtually none.

Speculation about the relation between endocrine syndromes and nonendocrine tumors have been made by Williams[20] and Bennett.[5] The syndromes are always associated wtih specific tumors. The tumors are believed to arise from the primitive foregut and morphologic similarities within the group are evident. The group includes the oat cell bronchogenic carcinoma, epithelial thymoma, medullary thyroid cancer, islet cell pancreatic cancer and carcinoid tumors of the bronchus, stomach and pancreas. The midgut tumors,

on the other hand, produce the carcinoid syndrome due to production of 5-hydroxytryptophane.

The question why this particular group of tumors causes endocrine syndromes has not been resolved. It is not hard to imagine that the abnormal DNA production of primitive malignancies could produce abnormal messenger RNA that would transcribe the production of "nonsense" peptides by ribosomes, akin to the errors produced in bacterial protein synthesis by certain antibiotics. When the chaotic protein synthesis of malignancies is considered, the random production of unusual peptides becomes feasible.

The present case involves the production and secretion into the blood of an exocrine enzyme by a tumor. For some completely unknown reason, this small cell carcinoma produced a substance for which there was no responsive end-organ or substrate. The function of amylase is to catalyze the simplification of starch into mono- and disaccharides. Amylase production by salivary glands and the pancreas are exocrine functions—secretion of a substance into the external milieu to perform a task in proximity to the excretion site. The syndromes previously described related to neoplasms are due to production of endocrine-like substances secreted into the blood. These substances are detectable because of their action as trophic substances or their effect on appropriate end-organs. The production of an exocrine substance with secretion into the blood is without discernible effect on the patient and the process is discovered by accident. The production of amylase by this group of malignant tumors is therefore of no particular consequence to the patient. The only foreseeable problem relates to the fact that the inadvertent detection of high levels of serum or urinary amylase may contribute to diagnostic confusion.

Conclusion

A case of bronchogenic small cell carcinoma producing the enzyme amylase has been described. Prolonged hyperamylasemia was documented for five months and assays of tumor tissue at autopsy revealed the tumor to be the source of the amylase. Other sources of hyperamylasemia were excluded. The exocrine enzyme in the blood produced no effect on the patient, and the possible diagnostic confusion created by the accidental discovery of elevated serum or urine amylase was discussed.

Acknowledgment

Gratitude is expressed to Drs. Merle S. Mark and W. Philip Eder for permission to use their case and to Robert C. Wong, Ph.D. for technical assistance in performance of tissue amylase assays.

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Bladder Cancer in Man

An Update

R. C. KOLOSSEUS, M.D.;* E. E. FRALEY, M.D.* and C. E. BLACKARD, M.D.*

Bladder cancer in man remains one of the most difficult and challenging problems in medicine. Herein are some of the recent clinical and laboratory developments which may eventually lead to advances in this disease.

CANCER OF THE bladder is a common tumor in man and accounts for approximately ten thousand deaths each year in the United States. Despite extensive efforts, most attempts to improve overall survival in this disease have been unsuccessful. There are both some exciting recent developments in the research laboratory as well as new clinical approaches which may lead to new advances in this disease.

Etiology

The etiology of most bladder cancers is unknown. However there are several chemical compounds which are suspected of causing human bladder cancer.[1] The aromatic amines 2-naphthylamine, benzidine, and 4-aminodiphenyl, byproducts of the aniline dye chemical industry, are believed to be carcinogenic in man because aniline dye workers have a high incidence of bladder cancer. Other compounds under investigation as causes of bladder cancer are phenacetin and non-nutritive sweeteners such as saccharin and sodium cyclamate.[1] Brown, Price, Satter and Wear[2] found that 50% of a group of patients with bladder cancer with no history of exposure to industrial amines excreted elevated amounts of tryptophan metabolites in the urine. They found that administration of pyridoxine partially corrected this abnormality in most of their patients. Patients with bladder cancer who had a history of exposure to industrial amines had normal tryptophan metabolism.

Cigarette smoking in males has been linked to bladder cancer. The results of four retrospective and two prospective studies concluded that the incidence of bladder cancer in moderate to heavy male smokers was from 1.9 to 3.3 times that in the general population of non-smokers.[1]

The association between bilharzial infestation of the bladder and bladder cancer has been recognized for a long time. However, the mechanism by which *Schistosoma hematobium* may induce bladder cancer is not clear. Gazayerli and Koraitum[3] believe the cancer may result from bladder outlet obstruction from the parasitic infestation resulting in degrees of urinary retention and concentration of carcinogenic agents in the urine.

In 1973, an RNA virus resembling those that are known to cause tumors in animals was isolated from transitional cell tumors of the human urinary tract.[4,5] Virus-like particles have been observed in human urothelial tumors in early passage tissue culture cells from these tumors. Furthermore, patients with urothelial tumors have antibodies in their serum to this virus. Recently it has been shown that tissue culture fluids of transitional cell tumors can produce maligant in vitro transformation of a variety of mammalian cells growing in tissue culture. Whether this virus plays any role in the pathogenesis of tumors in man is an unresolved question.

Factors Affecting Treatment and Prognosis

Most bladder tumors arise from the transitional cell lining of the bladder and 90% of these are transitional cell carcinoma.[6] There is a small percentage of squamous cell and adenocarcinomas. Squamous cell carcinomas usually are associated with poorer prognosis. Broders[7] was the first to correlate the degree of anaplasia of tumors with prognosis. He developed a system of grading the

*Department of Urologic Surgery, University of Minnesota Health Sciences Center and Veterans Administration Hospital, Minneapolis, Minnesota.

tumors I-IV according to the degree of anaplasia. Mostofi[6] has pointed out, that even a 'benign' papilloma may recur and patients with such papillomas often develop other tumors that are more anaplastic. Nichols and Marshall[8] found that 17% of patients having had the diagnosis of benign papilloma went on to develop carcinoma. Greene et al[9] found a similar situation in their patients. Survival has been shown to be better in low grade than in high grade tumors.

The depth of infiltration of the tumor into the bladder wall has been shown to be a more reliable index of prognosis. Jewett and Strong[10] were the first to show this correlation pathologically. Marshall's[11] modification of Jewett and Strong's classification is the one most widely used today and is shown in Table 1. Generally the Stage O, A and B_1 tumors have greater survival with any method of treatment than the B_2, C and D staged tumors.

TABLE 1
Marshall's Modification of Jewett and Strong's Method of Staging Carcinoma of the Bladder by Depth of Infiltration into the Bladder Wall

Stage of Tumor	Depth of Infiltration
O	Limited to mucosa
A	Not beyond submucosa
B_1	Not more than halfway through the muscularis
B_2	More than halfway through the muscularis but not into perivesical fat
C	Into perivesical fat but not involving the substance of adjacent organs
D_1	Invading substance of adjacent organs (including prostate), and/or metastatic to pelvic lymph nodes
D_2	Metastatic beyond the pelvis

Recent studies on human urothelial tumors have shown that patients have both a cell-mediated and humoral anti-tumor response to their tumors.[12] As with other human tumors, the patient's humoral response may also 'block' the anti-tumor activity of the patient's lymphocytes.[12] In a recent study, Hakala and Lange[13] have shown that the sera of certain patients with transitional cell cancers of the urinary tract have antibody that 'enhances' the killing of in vitro propagated human urothelial tumor cells by lymphocytes.

Another concept that is emerging from research in tumor immunology is that the patient's prognosis may be related to the degree of cell-mediated cytotoxicity displayed by the patient's lymphocytes as measured in vitro. For example, patients who consistently lack antitumor lymphocyte mediated cytotoxicity have a uniformly poor prognosis.[12] Thus if the current techniques of tumor immunology can be standardized and made reliable, they may be useful in predicting a patient's course.

Treatment

Bladder tumors are diagnosed and staged by transurethral resection and biopsy of the bladder. It is important to obtain bladder wall muscle in the biopsy specimen for pathologic staging. A bimanual pelvic examination under anesthesia is done at the time of biopsy to determine the size and degree of fixation of the tumor to surrounding pelvic structures. In addition pelvic angiography has been highly accurate in diagnosing extravesical tumor extension.[14] Depending upon the clinical and pathological staging, bladder tumors are treated as described herein.

Superficial (Stage O-A) Tumors

These tumors usually are best treated by transurethral resection alone. Only in cases where the entire bladder is covered with these tumors, and the tumors recur very rapidly after resection, are more radical forms of surgery, such as cystectomy, considered.

Because these tumors are multicentric, frequently recur, and may be present in a subcystoscopic phase, topical chemotherapeutic agents have been instilled into the bladder for both treatment and prophylaxis of recurrent superficial tumors. Veenema et al.[15] reported in their series using thio-TEPA that one third of the patients had tumor destroyed completely. They used 60 mg. of thio-TEPA in 1-2 oz. of water instilled in the bladder and retained for two hours. This was done weekly for four weeks. Veenema et al. later showed a decrease in the number of recurrences in patients with a history of recurrent tumors prior to the initiation of therapy.[16] When thio-TEPA instillations are being used, a pre-treatment white blood count and platelet count should be done because toxicity is manifest in bone marrow depression.

Invasive Tumors (B,C,D)

Once the diagnosis of an invasive bladder tumor is made, the choice of treatment lies between some further surgical procedure, external super-voltage radiation, chemotherapy or all three. Representative series of survival statistics for invasive bladder tumors with the various

modes of treatment are shown in Table 2. Irrespective of the type of treatment as mentioned herein, survival with B_1 lesions is significantly greater than with more invasive lesions.

TABLE 2
Representative Series of Five Year Survivals with various Modes of Treatment of Invasive Bladder Cancer

	Stage of Tumor			
	B_1	B_2	C	D
Partial Cystectomy Jewett et al[17]	58%	16%	16%	—
Simple Cystectomy Jewett et al[17]	50%	16%	12%	—
Radical Cystectomy Whitmore & Marshall[25]	47%	17%	13%	4%
Supervoltage External Radiation Caldwell, Bagshaw & Kaplan[21]	48%	25%	15%	—
Combined Preoperative Radiation & Cystectomy Whitmore et al[22]	40%	—37%—		

There are several different approaches to the treatment of invasive bladder cancer as follows:

1. Partial cystectomy—Partial cystectomy or segmental bladder resection is often used when the tumor is located on the dome of the bladder away from the trigone and ureteral orifices and is freely mobile. One of the disadvantages of this procedure for invasive tumors is the high incidence of local recurrences. Jewett et al.[17] reported a 25% recurrence rate and that 72% of the recurrences were of a higher grade and 28% were more deeply invasive than the original tumors. Another disadvantage of partial cystectomy is brought out by Baker.[18] In sectioning cystectomy specimens, he found that in Stage B_1 lesions, one out of five bladders had lymphatic spread of the tumor in the muscle layers of the bladder beyond the margins of the gross lesion. In Stage B_2 specimens, the average extent of lymphatic tumor spread was 60% of the bladder area and several specimens had regional nodal involvement. For these reasons, we recommend early cysteetomy for invasive bladder caneer. Other factors favoring the decision for early cystectomy are increasing histologic grade, multiplicity, diffuseness and rapidity of recurrences.
2. Total Cystectomy—Total cystectomy is the primary curative surgical procedure for invasive bladder cancer. This operation consists of removing the bladder and prostate in the male, and uterus, ovaries, tubes, and urethra in the female accompanied by ileac urinary diversion. Survival figures for the different stages are comparable for simple and radical (removing the regional pelvic lymph nodes and perivesical tissue en bloc) cystectomy. However, several points in favor of radical cystectomy over simple cystectomy have been recorded recently. Dretler et al.[19] had two groups of patients who had Stage D_1 lesions by virtue of pelvic lymph node involvement alone. Those who had only one or two nodes positive for tumor had a 33% five year survival with radical cystectomy. Three of these patients were clinically staged B_1 and would have had no chance of survival with a simple cystectomy. Four of these surviving patients had no grossly palpable pelvic lymph nodes supporting the view that the absence of palpable nodes should be an inducement rather than a deterent to lymph node dissection.

   Grimes et al.[20] reported an 18 per cent operative mortality in 39 patients after one-stage cystectomy and diversion and no operative deaths in fourteen two-stage procedures. We advocate the two-stage operation in which ileac diversion and staging are done first, followed in three to four weeks by radical cystectomy. This is especially recommended in males where cystectomy is a more formidable procedure.
3. Radiation—Radiation in the form of supervoltage external beam or Cobalt radiation is being used widely as a curative modality in invasive bladder cancer. The major drawback to the evaluation of radiation therapy for cure is the lack of accurate pretreatment pathologic staging of the tumor. In one of the larger series from Stanford,[21] only four of 215 patients had been surgically staged prior to treatment. While overall survival figures have been comparable to cystectomy[21] there is a high incidence of recurrent or persistent disease. The incidence of persistent morbidity from radiation cystitis is far from negligible.[21]

   Preoperative radiation has been used in the hope of reducing tumor size and sterilizing lymph nodes to prevent operative dis-

semination of tumor. Whitmore et al.[22] have shown an increase in survival in Stage B_2 and C tumors using 4000 R of Cobalt[60] over four weeks followed by cystectomy one to three months later. The five year survival in this group of patients has been increased from 17% with surgery alone to 37% with preoperative radiation. Other authors are in agreement that this treatment may be more effective than surgery alone in Stage B_2 and C lesions. On the other hand, two large cooperative studies[23,24] found no difference in survival in any stage of the disease with preoperative radiation.

Metastatic Tumors

None of the presently available modes of treatment has proved to be beneficial in metastatic bladder cancer except for the rare case of limited regional lymphatic involvement.[19] Even invasion of tumor into the prostate gland produced no survivors in nine cases treated with radical cystectomy by Whitmore and Marshall.[25] Radiation therapy has shown similarly poor palliative results with metastatic tumor.[21]

Chemotherapy, most notably with 5-Fluorouracil, has been reported to produce objective responses in patients treated this way. Nevin et al,[26] treated 10 patients with 'advanced' bladder cancer with 6000-7000 R of radiation and pelvic arterial infusion of 5-Fluorouracil through bilateral indwelling hypogastric artery catheters for ten days. They noted objective response in tumor size in six patients and complete disappearance of tumor in four of these patients.

Many combinations of modalities have been tried with reports of variable degrees of success in Stage D tumors. What is needed are cooperative studies with large numbers of patients and randomized treatment selection with controls, utilizing pretreatment surgical staging to evaluate the full extent of the tumor. Without such studies the efficacy of the various modes of treatment for bladder cancer can never be adequately assessed.

Summary and Prospects for the Future

The uniformly poor prognosis for deeply invasive carcinoma of the bladder has not been changed appreciably by attempts to treat this disease with surgery alone, radiation alone, or combined radiation and surgery. In patients who require radical cystectomy, it appears that staged surgery, with the ileac diversion and the cystectomy being done as separate operations, may cause the lowest operative mortality especially in males. Whether staged operations will improve the overall survival of invasive tumors is not known.

Recent studies suggest that many patients with this disease have an immunologic response to their tumors which may either be directed against the tumor or which may enhance tumor growth. One of the true frontiers in bladder cancer is the tumor immunology laboratory, and it is from these research efforts that the next new techniques for controlling this disease probably will come.

Clinical and basic laboratory studies suggest that certain chemicals may be important in causing human bladder cancers. Recently an RNA virus that resembles viruses known to cause tumors in animals has been found in association with these cancers. If the role of specific etiologic agents such as chemicals and viruses can be defined, new approaches to early diagnosis and prevention of cancer of the bladder will be possible.

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16-26. Will be found on page 250.

Retroperitoneal Hemangiopericytoma

MICHAEL A. BESS, M.D.* and JOHN H. LINNER, M.D.,† F.A.C.S.

A case of primary retroperitoneal hemangiopericytoma is presented. Hemangiopericytomas are rare, vascular tumors of pericyte origin. Those arising primarily from the retroperitoneum are usually highly malignant. Clinical presentation of the retroperitoneal tumors is usually as an abdominal mass associated with vague symptoms. Diagnosis requires histologic tissue examination using connective tissue stains. Radical surgical excision is the treatment of choice. The role of irradiation and chemotherapy has not been well established. Local invasion, post-operative recurrence, and metastases are common with lung, bone, liver, and mediastinum being frequent metastatic sites.

HEMANGIOPERICYTOMA IS A rare vascular tumor first delineated as a distinct entity by Stout and Murray in 1942.[1] The primary retroperitoneal hemangiopericytoma is among the most aggressive of these tumors and presents a most challenging diagnostic and therapeutic problem.

Case Report

A 41-year-old white woman sought medical attention because of continuous left sided abdominal pain which she attributed to vigorous snow shoveling one month previously. Physical examination was unremarkable and Xray of the thoracic spine showed a slight compression fracture of T-7. She was treated symptomatically and improved. Three months later she again presented with pain and physical examination was again negative. Symptomatic therapy again resulted in improvement. She remained relatively asymptomatic until six months after the onset of her initial symptoms at which time she noted the onset of increasing left upper quadrant discomfort, early satiety, and fatigue. There was no history of melena or weight loss. Physical examination revealed a healthy appearing woman. The blood pressure was 120/80 mm Hg and without postural changes; pulse was 130 beats per minute; and the temperature was 98.6 degrees. Examination of the heart, lungs, and extremities revealed no abnormality. There was no adenopathy. The abdomen was hard and there was a large, firm, non-tender, non-mobile, non-pulsatile mass palpable in the left upper quadrant. Pelvic examination was normal. There was a single café-au-lait spot in the interscapular region.

The hemoglobin was 11.2 gm %; white count 14,000 with a slight left shift. Twelve channel chemistry screening, urinalysis, clotting studies, and ECG were all within normal limits. A stool test for occult blood and cervical cytology smears were negative. Chest Xray showed elevation of the left hemidiaphragm.

Upper GI series showed marked superior and medial displacement of the stomach. Barium enema showed inferior displacement of the splenic flexure of the colon. IVP delineated a left upper quadrant retroperitoneal mass. Scan showed an apparently normal liver and spleen. Angiographic studies revealed displacement of the aorta to the right, the spleen and splenic artery



Figure 1

*Phase D Medical Student, University of Minnesota, Minneapolis at the time of authorship.
†Clinical Associate Prof. Surgery, University of Minnesota, Minneapolis.

superiorly, and the left kidney inferiorly by a relatively avascular appearing mass (Figure 1).

At operation in August 1972, the tumor was found to be compressing the spleen superiorly and the left kidney inferiorly. The stomach, pancreas, and gastrocolic omentum were stretched tightly over the anterior surface of the tumor. The most significant attachment of the tumor was to the retroperitoneal musculature, primarily the left crus of the diaphragm and the origin of the left psoas muscle. En bloc resection of the tumor necessitated including the spleen, left kidney, left adrenal gland, and segment of the para spinal muscles. Frozen section diagnosis during the course of the procedure was interpreted as probable lymphoma or reticulum cell sarcoma.

Definitive pathologic studies including connective tissue staining revealed a 28x20x15 cm hemangiopericytoma which was markedly necrotic in its central portions. Origin of the tumor could not be identified. None of the organs resected showed tumor involvement.

Three weeks post-operatively, the patient began receiving a course of 5000 rads of cobalt external radiation to the left upper abdomen over a one month period. One week prior to the end of the radiation therapy the patient developed weakness, nausea, and vomiting. X-ray films of the chest showed nodularity and an infiltrate in the upper lobe of the left lung (Figure 2). A lung scan showed decreased perfusion to that area. Actinomycin D, methotrexate, and cyclophosphamide were begun with little change in the pulmonary lesions. Rapid, progressive deterioration followed, with a development of marked hepatomegaly. The patient expired six months post-operatively. Autopsy revealed local recurrence of the tumor with metastases to lymph nodes, liver, and lung.



Figure 2

Comment

Hemangiopericytomas are composed of capillaries surrounded by masses of spindle shaped cells.[1] Using culture techniques, these surrounding cells have been shown to have their origin from the perivascular cells described by Zimmerman[2] as pericytes. The extraluminal location of these cells, as demonstrated by silver connective tissue stains, separate the hemangiopericytoma histologically from the hemangioendothelioma in which spindle shaped cells are seen intraluminally.[3] While histologically similar in some respects to the complex glomus tumor, the hemangiopericytoma lacks the organoid features of that encapsulated neoplasm.[1]

The natural history of the hemangiopericytoma is difficult to assess since the literature regarding the clinical course of the tumor is composed largely of events occurring after surgical excision. The biologic characteristics of the tumor are disturbingly diverse. There are no criteria which permit one to predict the behavior of an individual tumor.[4] The tumors may pursue a relatively benign course, infiltrate locally, or metastasize widely and rapidly.[5-7] Tumor without evidence of metastasis for as long as 30 to 60 years, in the absence of surgical intervention, occurs rarely.[5,6] A wide range of clinical tumor behavior has been noted in cases diagnosed by biopsy and treated with irradiation. Five year survival following surgical intervention occurs and is dependent not only on technique but also the biologic characteristics of the tumor.[8-12]

Since hemangiopericytomas may occur anywhere capillaries are found, it is not surprising that such tumors have been found in the extremities,[13] central nervous system,[14,15] thoracic cavity,[16-18] and intra-abdominally;[19] as well as in a wide variety of other locations.[20,21] Intra-abdominally, the tumors are most commonly found in association with the genitourinary[22-24] and gastrointestinal tracts,[25,26] or as primary retroperitoneal tumors.[7,27-29]

The presenting features of this case are typical of those associated with most retroperitoneal hemangiopericytomas. The initial presentation, hower, may range from a painless abdominal mass to symptoms of small bowel obstruction. Retroperitoneal hemangiopericytomas presenting with episodic hypoglycemia have been reported.[30,31]

There are no characteristic angiographic find-

ings. Marked vascularity, tumor vessels, and tumor blush have been noted in some case reports.[32,33] The finding of a relatively non-vascular mass at angiography, as was the case in this patient, has also been reported.[34]

The diagnosis lies in histologic tissue examination using connective tissue stains to demonstrate pericytes lying outside the vascular sheaths (Figure 3). Unfortunately, the degree of malignancy of these tumors is difficult to determine by usual techniques. The mitotic index is an unreliable criterion.[4,27] It has recently been suggested that the degree of malignancy of an individual hemangiopericytoma may be related to the structural and ultrastructural characteristics of the tumor. Tumors with abundant, uniformly distributed, branching capillaries with open (although sometimes slit-like) lumina; flattened endothelial cells; scant collagen around the capillaries; and ultrastructurally well differentiated pericytes grow and metastasize (Figure 4) more rapidly than hemangiopericytomas lacking these characteristics.[35]

The clinical characteristics of non-uterine, extragastric, intra-abdominal hemangiopericytomas have recently been reviewed.[19] In almost all such tumors direct local invasion, recurrence after excision, and metastases occurred. Of five tumors from primary retroperitoneal origin on which follow-up data was available, four showed metastases early in the clinical course after surgery. Metastases occurs most frequently to lung, bone, liver, and mediastinum.[36]

Since the recurrence rate after simple excision is high and the growth pattern of a given tumor is histologically unpredictable, the treatment of choice for all hemangiopericytomas is radical, en bloc surgical excision.[19,37-39] Retroperitoneal hemangiopericytomas are almost always large before coming to surgery. Radical extirpation may be difficult or impossible due to the proximity of the tumor to vital structures. Excessive blood loss occurs due to the marked vascularity of the tumor.[7,40,41]

The role of radiation therapy and chemotherapy in the treatment of hemangiopericytomas has not

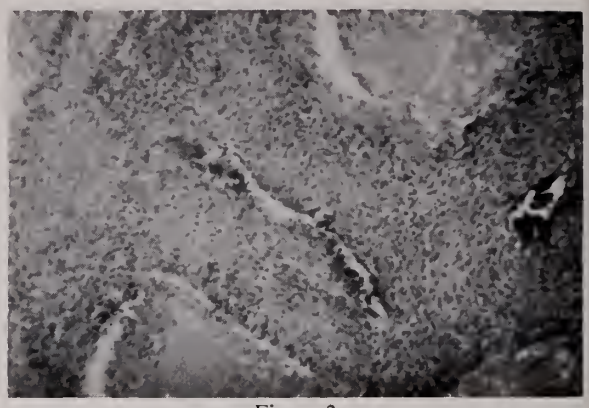


Figure 3

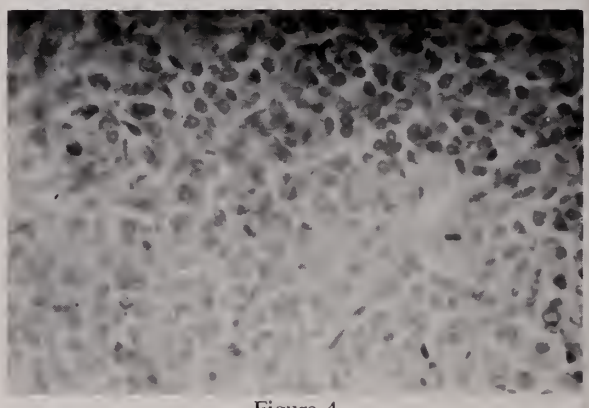


Figure 4

been well established, and few beneficial effects of radiation have been observed.[8,9,20] Chemotherapeutic agents have been used mainly with surgery and/or irradiation making objective improvement due to such agents difficult to evaluate. Probable objective improvement in bone metastases has been reported using methotrexate.[36] Similar results have been reported for pulmonary metastases using vincristine, actinomycin D, and cyclophosphamide.[42]

Intraoperative tissue diagnosis by frozen section is most desirable in differentiating the hemangiopericytomas from the more radiation-sensitive tumors, such as the lymphomas. This method of diagnosis may be inadequate, as in our case.

Acknowledgment

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6-42. Will be found on page 287.

Drug Induced Hemolytic Anemia

MICHAEL LOBELL, M.D.* and ROBERT WOODBURN, M.D.*

A patient with presumed Aldomet induced hemolytic anemia is presented. Because of the unusual clinical setting, corticosteroids were used to attempt to more rapidly reverse the hemolytic process after the drug was stopped. In this context, the clinical significance of the direct and indirect Coombs' test was reviewed and certain similarities between drug induced hemolysis of the Aldomet type and autoimmune hemolytic anemia were reviewed.

DRUG INITIATED ANTIBODY and complement coating of red cells can cause a spectrum of problems ranging from an asymptomatic positive Coombs' test to frank red cell destruction and anemia. It is the purpose of this paper to review drug induced hemolytic anemia, stressing pathophysiology, diagnosis, and therapy. The relationship of drug induced hemolysis to other autoimmune hemolytic states will also be discussed.

Case Report

The patient is a 63-year-old woman admitted in May of 1973 for coronary artery surgery.

In 1962 her blood pressure was 204/108. Since 1966 she had been taking 500-750 mgm. of methyldopa (Aldomet) daily. Her hemoglobin averaged 13.0 to 14.0 grams%. Four months prior to admission she had a typical inferior myocardial infarction following two weeks of recurrent chest pain. Antihypertensive therapy was interrupted at this time and re-started two months prior to admission. She was also treated with nitroglycerin and Isordil. Her Coombs' test had been positive for over three years. She continued to have anginal pain.

Her blood pressure on admission was 170/100; the hemoglobin, 13.4 grams with a hematocrit of 39%, MCV of 89, MCH of 30.7 and MCHC of 34.3. The red cells showed slight rouleaux. Two days preoperatively, her hemoglobin was 12.7 grams%, and there was no polychromasia. A single coronary artery bypass was done, using the patient's radial artery. Nine units of blood were used during surgery, and post-operatively her hemoglobin was 12.2 grams. The direct Coombs' test was strongly positive at 37°C and room temperature.

Seven days following surgery the hemoglobin was 8.8 grams% with normal indices and white count. One nucleated red blood cell was seen per 100 white cells, and there was slight polychromasia. The reticulocyte count was 2.5%, the red blood cell count, 2,870,000/mm^3. She was transfused with two units of packed cells and had a febrile response to one of them. During the next four days her hemoglobin varied from 9.5 to 10.5gms%, the reticulocyte count rose to 4.6%. Two weeks following surgery the hemoglobin began to gradually drop to 8.5 gms%, finally to 7.8 gms%. She received no further transfusions, the hemoglobin during the following week stabilized at this level, although the reticulocyte count rose to 8.5% on several occasions; polychromasia and increased platelets were present.

The serum reacted with most of a panel of red cells, no specificity could be determined. An eluate prepared from the patient's cells reacted to a 1:64 dilution with all panel cells. Thirteen days post-operatively the total bilirubin was 1.7 mgm%, with a direct bilirubin of 0.2 mgm%. Blood cultures were negative. Methyldopa had been discontinued three days prior to surgery, but during the hospitalization she received numerous drugs, including Lasix, Digoxin, barbiturates, Keflex, Valium, Dalmane and Dicoumarol. Sixteen days postoperatively she was started on oral Prednisone, 40 mgm. daily, because of the Coombs' positive anemia. There was little change in her hemoglobin when she was discharged on the 20th post-operative day.

Four days following discharge the hemoglobin had risen to 11.6% and the reticulocyte count was 7.9%. The Prednisone was tapered and discontinued. The indices remained normal and the mean corpuscular volume was 92 cubic micra. One month following discharge the hemoglobin was 13.0 grams%.

Our patient presented with a warm antibody, Coombs' positive (direct type) hemolytic anemia which closely resembled classical autoimmune hemolysis. Since she had been taking Aldomet when the hemolytic episode occurred and had a positive direct Coombs' test for three years, a causal relationship was suggested between the

*Clinical Hematology section, department of Internal Medicine and Clinical Pathology sections, United Hospitals, Miller Division.

Reprint requests: to Dr. Michael Lobell, United Hospitals, Miller Division, 125 West College Avenue, St. Paul, Minnesota, 55102.

Aldomet and the acute hemolysis.[1,2] Cessation of the drug and the institution of steroid therapy coincided with the reversal of the anemia.

Discussion

Pathophysiology of Drug Sensitization

The knowledge of which type of Coombs' antiserum is being used may help differentiate the type of drug reaction. Coombs' antisera can be obtained in three variations: (1) an anti-gamma type that reacts only with gamma-globulin coated cells, (2) an anti-complementary type that only reacts with complement coated cells, and (3) a broad-spectrum type that reacts with both gammaglobulin and complement.

Drugs produce four known types of red cell sensitization resulting in a positive direct Coombs' test: (1) The hapten type, (2) The "innocent bystander" type, (3) The methyldopa (Aldomet) type, and (4) The Keflin type, which results in a non-specific red cell protein coat and a positive Coombs' test, but only very rarely in hemolysis.[16,3,4] The hapten type occurs classically in patients receiving large doses of intravenous penicillin, in the order of 10 million units per day.[5] Oral penicillin does not reach the concentration needed to produce hemolysis. Penicillin, acting as a hapten, binds strongly to the red cell membrane, and reacts with a 7S IgG (warm) penicillin antibody. Although 90% of the patients receiving penicillin can develop antibodies, only a small percentage develop the 7S antibody that results in a positive Coombs' tests and hemolytic anemia. Only Coombs' serum that has antigammaglobulin activity (the first and third varieties above) will produce a positive test. Complement fixation is usually not involved in this reaction.[17] This type of coated erythrocyte is removed from the circulation by the reticuloendothelial cells in the spleen and liver. Figure 1 depicts the hapten type of drug sensitivity.

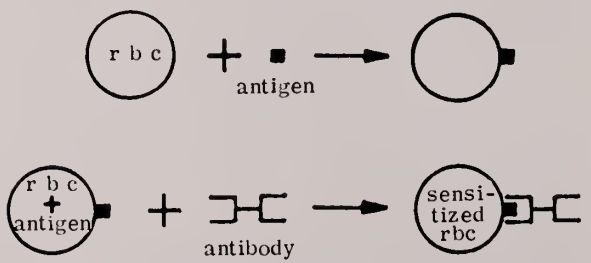


Fig. 1—The Hapten mechanism. The red cell and antigen, such as penicillin, combine and provoke an antibody response. The globulin antibody is directed against the drug (penicillin) which is bound to the red cell membrane.

The second type of drug red cell reaction, the so-called "innocent bystander" type, occurs with a drug that has only mild affinity for red cells.[6] Some of these drugs are Stibophen, Sedormid, Quinidine and Quinine. In those rare people who can form an antibody to the drugs in this class, the drug and antibody tightly complex in the blood stream and then, because of the drug's mild affinity for the red cells, the entire complex attaches to the red cell membrane. This reaction is a complete non-hapten type and therefore the complement fixing sequence is activated. Complement becomes attached to the red cell membrane and remains there, although the drug-antibody complex may detach itself later. Complement coated cells can lyse directly in the vascular compartment, or more commonly, may be recognized by the reticuloendothelial system as foreign and be engulfed and destroyed. Anticomplementary Coombs' sera will produce a positive test with these cells. Figure 2 depicts the "innocent bystander" type of reaction.

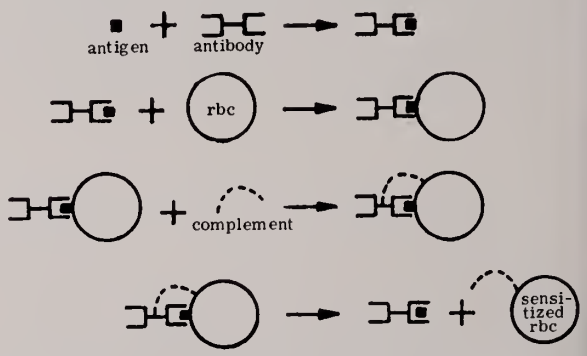


Fig. 2—The innocent bystander mechanism. The antigen and antibody combine and loosely attach to the red cell (or simply activate the complement system in plasma surrounding the red cells). Complement is fixed to the cell and the antigen antibody complex freed. The complement coated red cell is predestined to destruction.

The third reaction, the Aldomet type, has also been noted to occur with levodopa, mefenamic acid and chlordiazepoxide. This was apparently the mechanism of hemolysis in our patient and occurs in about 20% of patients who are treated with Aldomet. It is variously estimated that only 0.1% to 2.0% of these sensitized patients develop anemia, although more will have a reticulocytosis indicative of a compensated hemolysis.[7,8,18,19]

This drug reaction appears to alter the body's immune system either by altering the red cell membrane so it is not recognized as normal to

the body, or by altering antibody-forming cells to produce antigen capable of destroying normal red cells. In either case a warm antibody (an IgG) is produced and attaches to the red cells; this may cause hemolysis by a mechanism that is very similar to autoimmune hemolytic anemia.

In some cases the antibody has Rh specificity, and in other cases, such as this case, it is nonspecific and has general activity against all red cells. Even in those cases where the circulating antibody reacts against all red cells, it appears there is an Rh genetic locus involved, because if the patient's antibody is reacted with red cells from those very rare persons with no Rh locus (Rh null individuals) no reaction takes place, showing that some kind of Rh dependency is present. Figure 3 depicts the Aldomet reactions that lead to hemolysis.

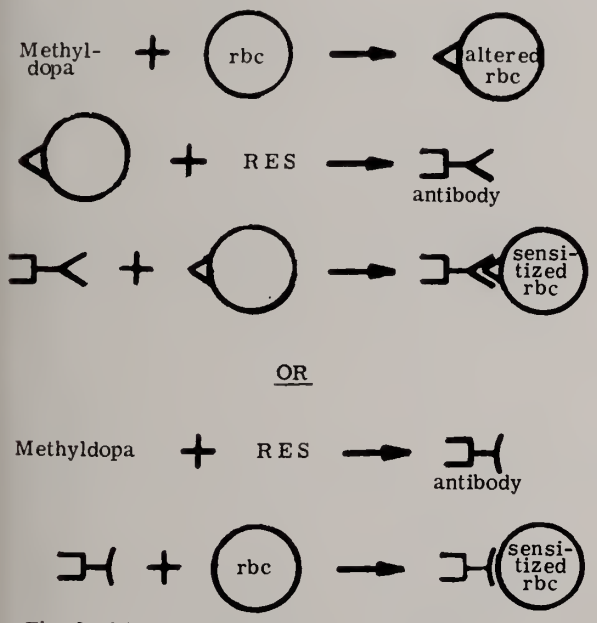


Fig. 3—The Aldomet reaction. Methyldopa either attaches to the red cell membrane and produces an antibody response to the combination, or acts as a direct stimulator of the reticuloendothelial system, provoking in either case an Rh-like antigen to the red cell.

Diagnosis and Relationship to AIHA

It is apparent that a number of drugs may cause a positive direct Coombs' test and hemolysis may ensue at any point during the course of therapy.

In the hapten (penicillin) type of reaction a Coombs' test is always strongly (4+) positive. Complement is not fixed and this is a key point in differential diagnosis, especially when complement fixing autoimmune diseases are a part of the differential diagnosis. Diagnosis of penicillin induced hemolysis can be further confirmed by standard serologic procedures using the prototype of the indirect Coombs' test. Penicillin sensitive erythrocytes are prepared by incubation and reacted in the offending patient's serum to produce agglutination. Normal sera, or a control, will give no reaction since the specificity of the antibody is against penicillin and not toward an antigen intrinsic to the red cell membrane. Absolute (though unnecessary) confirmation could be accomplished by testing an eluate of the patient's cells and reacting this with penicillin sensitive erythrocytes.

The "innocent bystander" type of reaction should be suspected when hemolytic anemia develops with drugs known to affect the red cell. The Coombs' test, again, will be positive, but since complement is fixed by this type of reaction, anticomplementary Coombs' sera will give the strongest reactions. In vitro confirmation studies employ the principle of the indirect Coombs' test, incubating the offending drug with the patient's serum and red cells. Again, the indirect Coombs' test is negative unless the responsible drug is added to the incubation mixture, since the antibody is directed against the drug and not the red cell membrane.

Differentiation of drug-immune hemolytic anemia of the Aldomet type (DIHA) from autoimmune hemolytic anemia (AIHA) may be difficult. Some AIHA can be impossible to differentiate through laboratory determinations and both diseases have positive broad spectrum Coombs' tests. The relationship of Aldomet DIHA to AIHA will be reviewed in the following discussion.

In general, one can distinguish three clinical syndromes which are characterized as AIHA: (1) warm antibody hemolytic anemia (2) cold agglutinen hemolytic anemia, and (3) paroxysmal cold hemoglobinuria. The majority of AIHA problems (Table 1) relate to the warm antibody type (warm and cold not only refer to specific syndromes, but in the laboratory also refer to the thermal range of maximal reactivity) (Tables 1 and 2).[9]

Hemolytic anemia due to an IgG warm reacting antibody is characterized by the rapid onset of anemia, usually associated with splenomegaly. Since there is a fairly high association with other autoimmune diseases (lupus, etc.), cancer and lymphoma, the clinical course will be altered by variable physical findings that reflect the under-

lying disease. The Coombs' test is usually strongly positive and complement is usually fixed so that the anticomplementary Coombs' test is also positive, but less strongly so since IgG has only a limited capacity to bind complement.[10] With this in mind, should a patient develop hemolytic anemia while on Aldomet, there may be no serological way to differentiate this process from warm antibody AIHA, since both are of the warm antibody type, will give a positive direct Coombs' test with IgG, broad spectrum and anticomplementray antisera, and both may or may not have Rh specificity. Diagnosis may depend on simply withdrawing the drug to see if hemolysis subsides.

The syndrome of hemolytic anemia due to a cold reacting (IgM) antibody usually differs from that due to a warm reacting antibody in several respects. Usually it is a disease of elderly people (except when virus or a tumor is associated). The anemia is chronic, low grade and worse in the winter. Physical findings depend on the underlying disease, though splenomegaly is frequently present. The anticomplementary Coombs' test is usually moderately to strongly positive since IgM is capable of binding a large amount of complement. Cold agglutinin titers are usually over 1:1000 (Table 2). If further characterizations are necessary, cold agglutinins produce a stronger Coombs' test when the test is done at room temperature and when the blood is kept at 37°C.

The Mechanism of Hemolysis

The mechanism of destruction of antibody coated red blood cells is not completely understood. Except for very rare cases when there is rapid immediate cell lysis due to complement mediated and antibody mediated red cell destruction (paroxysmal cold hemoglobinuria, transfusion reaction, some cases of paroxysmal nocturnal hemoglobinuria), red cell destruction occurs mainly in the reticuloendothelial system and predominently in the spleen.[11,12] Several authors have noted that red cells covered with IgG antibody, but not with IgM antibody, or complement components, become attached to monocytes, either those in the peripheral blood or more significantly, those in the spleen. Cells may be completely destroyed or the cell membranes fragmented with the production of spherocytes.[13] These spherocytes are small and more rigid than normal red cells. They can be more easily trapped in the splenic sinusoids and further exposed to attack by monocytes and macrophages, as well as exposed to loss of viability due to metabolic changes. The amount of antibody on the cells is related to the area where the cell is sequestrated (light sensitization—spleen,

TABLE 1

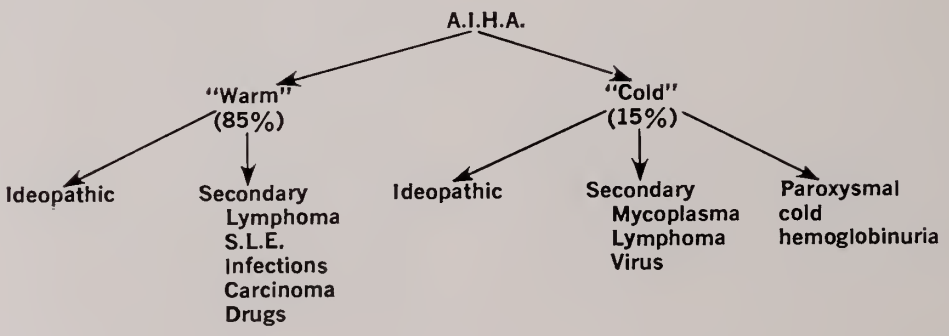


TABLE 2

	Warm antibody AIHA	Cold Agglutinin Disease	Drug-induced anemia
Optimum temperature	37°	4°-25°	Variable
Specificity	Rh and non-specific	Usually anti I	None or Rh
Coombs' reaction[9]	IgG alone—30% IgG & complement—50% Complement alone—20%	Complement	Depends on specific drug

heavy sensitization—spleen and liver) and also to the rate of hemolysis.[14] Far less is known about hemolysis with IgM cold antibodies. IgM does not appear to cause adherence of red cells to monocytes, although phagocytosis apparently is a major cause of hemolysis. Red cell destruction occurs predominently in the liver, and, to a lesser extent, in the spleen.

Therapeutic Considerations

The type of thermal antibody that is present may relate to the effectiveness of therapy. Steroids, which generally produce RE blockade, and splenectomy are important therapeutic considerations in warm antibody hemolytic anemia and are generally quite effective. However, the procedures are of equivocal benefit in cold antibody hemolysis. Frequently the cold antibody hemolytic diseases are best treated by directing therapy against the underlying diseases and avoiding cold exposure.

When the antibody response is to a drug, stopping the offending agent will result in cessation of hemolysis. Penicillin hemolytic anemia is always due to huge intravenous doses of penicillin, so a switch to oral penicillin or another antibiotic will stop the hemolysis. Unfortunately, Aldomet hemolytic anemia may continue for a variable period of time after the drug has been discontinued. In our patient the precarious clinical situation and difficulty in correctly crossmatching blood led us to use adrenal corticoids with resultant rapid improvement of the hematocrit. However, adrenal corticoids are rarely indicated, since stopping the drug is usually all that is necessary. Two additional points regarding Aldomet should be again stressed. First, a positive direct Coombs occurs frequently, but clinical hemolysis is rare so the presence of a direct Coombs often does not require discontinuance of the drug. Secondly, following cessation of Aldomet, the Coombs' test may be positive for months and the hemolysis may continue for weeks, albeit at a lower level of cell destruction.

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Cover Painting

"Magic Forest"

Dr. Robert O. Fisch painted the cover picture in the Spring of 1974. It is a gouche water color. He told the editor that the "Magic Forest" represents the imaginative dream world about a forest at spring.

Dr. Fisch is an Associate Professor in the Department of Pediatrics, University of Minnesota Medical School, and has as his hobbies painting and photography. He has studied art at the Academy of Fine Arts in Budapest, the Walker Art Center in Minneapolis, the University of Minnesota and, most recently, the Minneapolis College of Art and Design. His works have been exhibited in various one-man and group shows.

Staphylococcal Endocarditis in Narcotic Addicts

Diagnosis and Treatment

MOHAMMED Y. KHAN, M.D.,* WENDELL H. HALL, M.D.* and
DALE N. GERDING, M.D.*

Sixteen narcotic addicts with staphylococcal endocarditis were admitted to three Minneapolis-St. Paul hospitals between 1968 and 1973. Presenting features were fever, septic pulmonary infarcts, cardiac murmurs, occasionally arthritis and peripheral emboli, and rarely a pericardial rub. Nine patients had murmurs suggesting tricuspid valvular insufficiency, two had mitral insufficiency, one aortic insufficiency, and four had no murmurs. Staphylococcus aureus was the infecting organism in every patient. In one patient, staphylococcus of nearly identical phage type was cultured from the blood, skin lesions and heroin powder used by the patient. Fifteen patients received therapy and all survived. One unrecognized patient with no murmurs expired without antibiotic therapy.

INFECTIVE ENDOCARDITIS frequently complicates addiction to intravenous heroin. In the last five years, 16 addicts with this condition were observed in three Twin City Hospitals. Because of its unusual features, this form of endocarditis may not be promptly recognized and treated. This review may aid in early diagnosis and treatment. All but one of our 16 patients were quickly recognized and treated, and their endocarditis was cured.

Material

The cases in this study included all instances of infective endocarditis between 1968 and 1973 among narcotic addicts at the Hennepin County General Hospital (13 patients), Minneapolis Veterans Administration (two patients) and St. Paul-Ramsey Hospital (one patient). Eight of these 16 patients were seen in the last year. The diagnosis was usually made because of fever, repeated positive blood cultures, cardiac murmurs, and pulmonary or peripheral emboli.

Results

Our cases occurred sporadically without evidence of a common source of infection. Their average age was 33 years (range 19-47). There were five women and 11 men. Every patient injected either heroin (13 patients) or amphetamine, cocaine, or hydromorphone (Dilaudid) (one patient each) by the intravenous route. A summary of their presenting symptoms is shown in Table 1. All patients had fever and chills. The duration of illness before admission was one to seven days (average four days). The initial temperature ranged from 101° to 106°F. The patients became afebrile within three to seven days after beginning appropriate antimicrobial therapy. Dyspnea and pleuritic chest pain were also common (87%). The coincidence of fever and acute chest symptoms often suggested an acute respiratory infection. Upper abdominal pain, present in nine patients, frequently led to an initial impression of an acute abdominal emergency.

Other nonspecific complaints (eight patients)

TABLE 1
Presenting Symptoms in 16 Patients

Symptom	No. Present
Fever and chills	16
Chest pain and dyspnea	14
Upper abdominal pain	9
Headache	8
Myalgia and arthralgia	8
Photophobia and nuchal rigidity	4

*Department of Medicine, University of Minnesota Medical School and Hennepin County General Hospital.
Reprint requests to: Dr. M. Y. Khan, Hennepin County General Hospital, Portland Avenue South at 5th St., Minneapolis, Minnesota.

included headache, myalgia, arthralgia, photophobia, and nuchal rigidity. These complaints implied meningitis, which was excluded by negative spinal fluid examinations in six patients. Other clinical conditions also considered were influenza, viral hepatitis, pancreatitis and septicemia.

The chief clinical findings are presented in Table 2. As mentioned before, fever was present in every patient. There was x-ray evidence of septic pulmonary infarcts in 13 patients. The lesions presented first as soft round or triangular infiltrates and later as circumscribed round densities. They were often multiple and bilateral (Figure 1), and in seven patients there was cavitation of some lesions (Figure 2). Despite extensive pulmonary involvement, there was complete clearing of all the lesions with antibiotic therapy.

TABLE 2
Clinical Findings in 16 Patients

Clinical Finding	No. Present
Fever	16
Multiple venous needle marks	14
Septic pulmonary infarcts	13
Cardiac murmurs	12
Arthritis with effusion	5
Peripheral emboli	4
Pericardial rub	2

Multiple needle marks over the antecubital fossa from intravenous narcotic abuse were observed in 14 patients. Two recent addicts did not show obvious needle marks. Clinical evidence of suppurative thrombophlebitis was not found in any patient.

Although there was no history of preexisting heart disease, 12 patients had detectable cardiac murmurs (Tables 2 and 3). Nine had murmurs suggesting tricuspid valvular insufficiency. Their murmurs were systolic and variously described as ejection or holosystolic, heard best along the left sternal border. Chest Xrays in all but one of the

TABLE 3
Cardiac Findings and Septic Emboli in 16 Patients

Valvular Murmur	No. of Patients	Pulmonary Emboli	Peripheral Lesions*
Tricuspid Insufficiency	9	8	2
Mitral Insufficiency	2	1	1
Aortic Insufficiency	1	0	1
No murmur	4†	4	3

*Includes arthritis, petechiae, splinter hemorrhages and metastatic abscess. (Some patients had several of these findings.)

†One patient died. Autopsy showed tricuspid valve vegetations and distant metastatic abscesses.



Fig. 1—Chest Xray showing early multiple pulmonary infiltrates (septic infarcts) characteristic of staphylococcal tricuspid valvular endocarditis in a heroin addict.

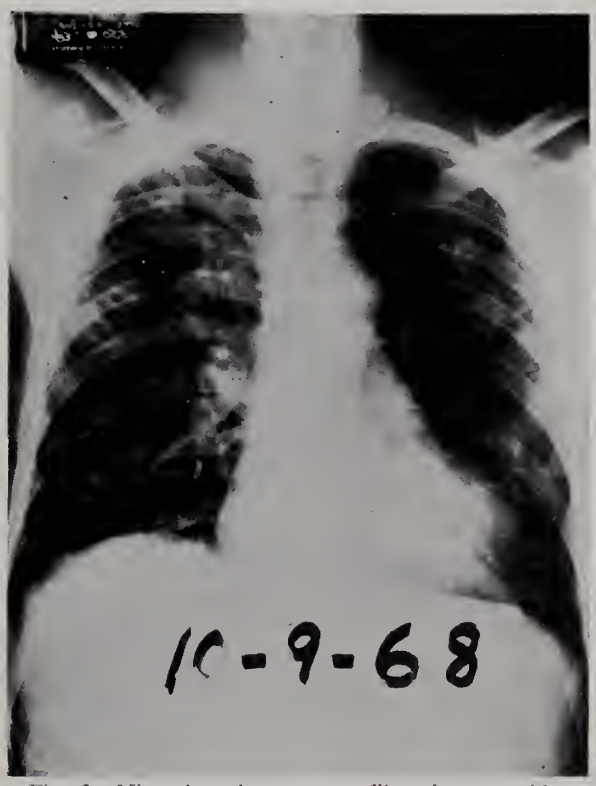


Fig. 2—Nine days later, x-ray film shows rapid response to antibiotic therapy, with resolution to circumscribed, sometimes cavitating lesions in both lungs.

patients with presumed tricuspid insufficiency showed evidence of septic pulmonary infarcts; two of these patients also had peripheral lesions, either arthritis or cutaneous petechiae. In two patients, there were murmurs characteristic of mitral insufficiency. In one patient aortic regurgitation developed on the fifth day in the hospital.

One of the four patients without murmurs died, and at autopsy one cusp of his tricuspid valve was found destroyed. He also had massive septic pulmonary emboli, multiple renal abscesses, and diffuse glomerulonephritis. This patient had *Staphylococcus aureus* in blood cultures and tricuspid valvular vegetations. The three remaining patients had x-ray evidence of septic pulmonary infarcts suggesting emboli arising from the tricuspid valve.

Five patients developed arthritis involving one or two large joints. Splinter hemorrhages, petechiae and metastatic abscesses were observed in four patients. A pericardial friction rub was heard in two patients. None of the 16 patients had a palpable spleen.

Complications

Congestive cardiac failure occurred in one patient with aortic valvular endocarditis. This patient recovered from failure with diuretics. One patient developed empyema; it was surgically drained with good results. Acute renal failure occurred in one patient. The patient recovered after hemodialysis.

Laboratory Studies

Anemia was observed in every patient; the leukocyte count on admission ranged between 6,000 and 22,000/cu mm (average 12,600/cu mm). The sedimentation rate was increased in seven patients. No hematuria was observed. Liver function tests were abnormal in nine patients.

S. aureus, coagulase-positive, was repeatedly found in blood cultures (three or more times) from every patient. In ten patients, the staphylococci were resistant to penicillin G when tested by the disc diffusion method (Kirby-Bauer), and in the remaining six patients the organisms were susceptible.

The antibiograms showed no consistent pattern among the 16 blood cultures tested. In three patients the staphylococci were typed with bacteriophages. In one the staphylococcus was phage type 42E/47/55. In the second patient the staphylococcal phage type was 52/52A/80/81. Heroin powder used by these two patients was not available for study. In the third patient, *S. aureus* phage type 54 was isolated from his blood and skin lesions and a dense growth of *S. aureus* phage type 47/54 alone was obtained from heroin powder used and provided by the patient. This phage typing indicated that there was no common source of infection in these patients. Contaminated heroin powder seemed to have been the source of the infection in the third patient. The spinal fluid was examined for bacteria in six patients, and the cultures were sterile. Joint fluid was obtained from three patients and showed no growth on culture. *S. aureus* was grown from pleural fluid in one patient with empyema.

Antimicrobial Therapy

Four patients with susceptible organisms received penicillin G in a dose of two million units every two hours. Because of allergy to penicillin, two patients with penicillin-sensitive organisms received cephalothin, eight to 12 grams per day intravenously. Nine cases were treated with a penicillinase-resistant penicillin (oxacillin or methicillin) in a dose of two grams every four hours. The latter antibiotics were administered intravenously by infusion (30 minutes) for four to six weeks. A decrease in fever and negative blood cultures were noted within three to seven days. Cardiac murmurs persisted in seven of 12 patients. No new murmurs appeared. All 15 treated patients were discharged without symptoms. Only one patient has returned for follow-up, and he continues to have aortic valvular insufficiency.

Discussion

Infective endocarditis, a serious complication of narcotic addiction, has been reported by many investigators.[1-15] It is being increasingly recognized in the U.S., where the incidence of narcotic addiction in young adults has become alarming. Endocarditis caused 8.7% of the deaths among narcotic addicts studied by the office of the Chief Medical Examiner in New York City.[5] Of 20,000 heroin addicts who live in the Washington, D.C. area, about 600 were admitted to the D.C. General Hospital in a four year period. Fifty (8%) were admitted for infective endocarditis, and their mortality rate was 28%.[12] The potential seriousness of this disease is emphasized by one report of a mortality rate of 70%.[6]

Cause of Endocarditis

The increased incidence of infective endocarditis in narcotic addicts is usually attributed to intravenous drugs given with little or no aseptic precautions. The drugs may also be contaminated when mixed with adulterants to increase their bulk. Lactose, commonly used as a filler, may enhance the growth of bacteria in the drug sample.[1] Abundant *S. aureus* was recovered in pure culture from heroin powder provided by one of our patients, and the phage type of the staphylococcus was similar to that of the strain recovered from his blood and skin lesions. We were unable to obtain drug samples directly from other patients to study further this problem. There have been other attempts to culture the organisms causing infective endocarditis in addicts from confiscated (police) supplies of narcotics and addict's injection equipment and they have failed.[13,16]

Types of Organisms

A wide variety of microorganisms has been the cause of endocarditis in narcotic addicts. The list includes staphylococcus, streptococcus, *Pseudomonas aeruginosa* and (rarely) Candida.[10-13,15] In recent large series, 40-70% were infected with *S. aureus*. This is in marked contrast to endocarditis in nonaddict populations, where staphylococcus is found in no more than 25%. *S. aureus* was the sole agent recovered from the 16 addicts reported here.

Site

Infective endocarditis in a nonaddict population rarely involves the tricuspid valve.[8,14] In narcotic addicts the tricuspid valve was affected in 40-76%.[8-15] One group differed in this regard, reporting that the most commonly affected valves, in order of frequency, were the aortic, mitral, and tricuspid.[7] Right-sided endocarditis can be easily missed. In some cases with tricuspid insufficiency a murmur may be difficult or impossible to detect.

Tricuspid Valve

On the basis of our own and other experience,[1-15] several characteristic features of infective endocarditis in narcotic addicts have been identified. First, previously normal cardiac valves are commonly involved. Second, the tricuspid valve is often infected. Because of the friable tricuspid valvular vegetations, the clinical course is often dominated by repeated episodes of septic pulmonary infarction. Third, systemic arterial emboli, commonly observed in left-sided endocarditis, may also occur when the tricuspid valve is involved. Fourth, staphylococci are the infecting organisms in most of these patients.

Therapy

The initial therapy must include a penicillinase-resistant penicillin or cephalosporin. Some authors[9,13] have found streptococci or *Ps. aeruginosa* are frequent causative agents. Intramuscular gentamicin has been recommended as a part of the initial therapy,[12] because it is active against both staphylococci and *Ps. aeruginosa*. When culture and antimicrobial susceptibility data are available, the most appropriate antibiotic can be selected and given parenterally for four to six weeks. The disease usually carries a good prognosis when it is promptly recognized and appropriately treated.

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Annular Pancreas in the Adult

RONALD OLIN, M.D.* and HENRY A. NORUM, M.D.*

A case of obstructive annular pancreas with associated alcohol-induced chronic pancreatitis in a 49-year-old man is described. This was successfully treated by vagotomy and gastro-jejunostomy. The incidence, embryology, pathogenesis, clinical features and radiologic characteristics are discussed.

IT IS UNUSUAL to attribute high intestinal obstruction in an adult to congenital causes. Annular pancreas is a rare congenital anomaly capable of producing mechanical obstruction of the duodenum. The malformation was given its name in 1862 by Ecker.[1] Ravitch & Woods[2] stated that "it is the only congenital anomaly of the gastrointestinal tract which usually produces symptoms later in life." Cases are generally classified as (1) neonatal, (2) pediatric, (3) adult-asymptomatic (an autopsy curiosity) and (4) adult-symptomatic. The ratio of adult to neonatal cases is approximately 4:1. Drey[3] reviewed 62 cases of adult-symptomatic annular pancreas and Dodd and Najis[4] described the radiographic characteristics.

Case Report

A 49-year-old male carpenter was admitted to hospital on February 29, 1970, because of ten days of upper abdominal pain and vomiting.

He had been told that he had a duodenal ulcer in 1961, but did well until May, 1963, when he was hospitalized elsewhere for one week because of high epigastric pains radiating to the back and vomiting of six weeks' duration. He drank beer moderately. Serum amylase levels were elevated. Xray of the gallbladder revealed normal function. An upper gastrointestinal Xray (Figure 1) revealed a "persistent spasm or irregularity of the descending duodenum with coarsened mucosal folds." A diagnosis of chronic relapsing pancreatitis and duodenitis was made. He was advised to abstain from alcohol and was dismissed on a bland diet and anticholinergic drugs. He was hospitalized three more times between 1963 and 1971 with similar episodes. An upper gastrointestinal Xray in October, 1968, (Figure 2) revealed "a marked delay in passage through the proximal duodenal loop in its second portion probably



Fig. 1—May, 1963.

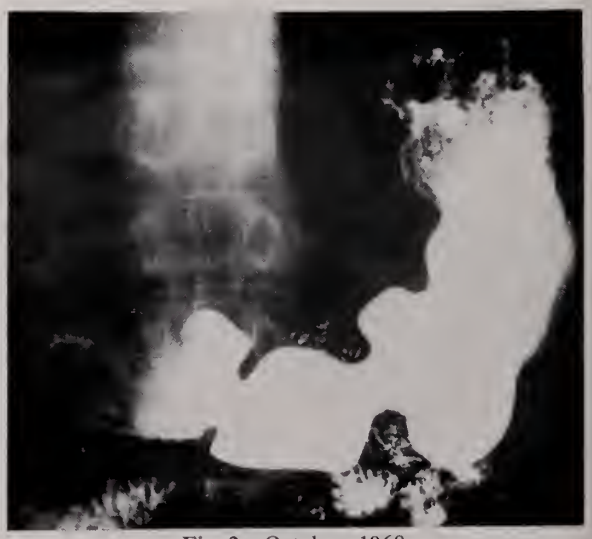


Fig. 2—October, 1968.

*Departments of Internal Medicine and Surgery Fargo Clinic Box 2067, Fargo, N.D.

secondary to pancreatitis."

During the last year before admission to hospital, he had abstained from alcohol. Since the onset of symptoms in May, 1963, he had lost 54 pounds in weight. Serum amylase and lipase levels were elevated; hemoglobin, leukocyte count, serum calcium and fasting blood sugar were normal. Tomograms of the pancreatic area revealed small calcifications in the region of the head of the pancreas. An upper gastrointestinal Xray (Figure 3) revealed considerable retained secretions, delay in gastric emptying and extrinsic pressure on the lesser curvature and proximal duodenum. The radiologist suggested a differential diagnosis of carcinoma of the pancreas, "aberrant" pancreas and pseudocyst of the pancreas.



Fig. 3—February, 1970.

With the diagnosis of pseudocyst of the pancreas with duodenal obstruction, the patient was explored. The stomach was flabby, thickened and twice normal size. The pylorus was patulous and the first portion of the duodenum was twice the usual diameter. There was a sausage-like mass around the descending portion of the duodenum having the appearance of an annular pancreas. The body and tail of the pancreas were edematous and had a hobnailed, coarse appearance. There was no evidence of neoplasia. Biopsies were not taken. The lesser curvature of the stomach was opened and the mucosa of the stomach and duodenum appeared normal. The second portion of the duodenum was narrowed and only admitted one finger. There was no ulceration in the second portion of the duodenum. A vagotomy and gastro-jejunostomy were done. The postoperative course was uneventful.

The patient was seen as an outpatient six weeks after operation and was asymptomatic. He had gained 14 pounds and was eating everything although in small amounts.

He wrote us four years later that he had felt well since surgery and had no further attacks of pancreatitis. He continued to abstain from alcohol, followed no particular diet and was taking no medications. He had regained weight to his pre-illness level.

Embryology

The pancreas develops from two buds off the midgut in the three to four mm. embryo before gut rotation occurs.[5] The posterior bud grows to the left giving rise to the tail, body and part of the head. The anterior bud forms the remainder of the head. Lecco's hypothesis[6] is the most popular. He theorizes that the failure of the tip of the anterior bud to rotate completely to the right and posteriorly with the duodenum results in a band of elongated pancreatic tissue embracing the duodenum circumferentially. In all recorded adult cases, the annulus is located either in the second portion of the duodenum or rarely at the junction of the first and second portions. The annulus consists of pancreas. Occasionally, the annulus is incomplete with a fibrous defect anteriorly at the point of fusion of the accessory tissue and the head of the pancreas. The duct of the annulus may open directly into the duodenum or in some cases drains either into the duct of Santorini or the duct of Wirsung.

Pathogenesis

In newborns and children, atresia of the duodenum often leads to obstruction. It is probably congenital in origin. In adults, duodenal atresia is not common and there is no satisfactory explanation for the development of duodenal obstruction later in life. It has been thought that the expansion of the duodenum is mechanically limited by the annulus. As a result, each food bolus as it is propelled by peristalsis through the duodenum causes pressure on the bowel wall as it is forced through the area of the annulus. Repeated local anoxia from pressure on the vessels in the bowel wall may lead to a fibroblastic reaction which leads to atresia. In Drey's series, 15 patients had associated acute or chronic pancreatitis and two had carcinoma of the head of the pancreas. Sixteen patients also had peptic ulcers (seven duodenal, four gastric, one post-bulbar and one gastric and duodenal). The 25% incidence of associated peptic ulceration was likely due to hyperacidity from retained gastric secretions secondary to duodenal obstruction. An inherent mucosal weakness or familial predisposition to ulcers may also be factors. The 25% incidence of associated pancreatitis in adult cases seemed to be related to alcohol ingestion and abuse. Alcohol is thought to produce a duodenitis with swelling of the ampullary region and resultant obstruction to the flow of pancreatic secretions.

Clinical Features[3,7,8]

Males are affected more commonly than fe-

males. There is no apparent racial predilection. It is primarily a disease of young adults between 20 and 40 years of age. The youngest patient reported was 17 years old and the oldest 74. The onset may be abrupt or gradual. Symptoms will depend on the degree of obstruction. The cardinal symptoms are pain and vomiting with nocturnal accentuation. The pain is primarily epigastric and crampy. Some patients also complain of post-prandial fullness and have relief with food or alkali. The vomiting is often "coffee-ground." Weight loss can range from zero to 30 pounds (usually five to 10). The duration of symptoms is usually five years or less (acute to 24 years).

Roentgen Criteria

In the newborn, an upright film of the abdomen reveals air-fluid levels in the dilated stomach and duodenum ("double-bubble sign"). In the adult, contrast studies are needed. Dodd and Najis have outlined the following criteria:

Proximal to the Annulus:

1. Dilatation.
2. Reverse peristalsis.
3. Pyloric incompetence, with or without gastric dilatation.

At the Level of the Annulus:

1. Medial displacement of the duodenum.
2. Notchlike pressure defect (1 to 3 cm. in length).
3. Mucosal effacement.
4. Bulging of the recesses on either side of the annular band.

Distal to the Annulus:

1. The lumen may be normal or diminished.

Lesions most frequently confused with annular pancreas are post-bulbar ulcers and duodenal neoplasms. Duodenal ulcerations at the level of the annulus have not been described. Diagnostic aids such as hypotonic duodenography, fiberoptic duodenoscopy and selective coeliac angiography may help to differentiate intrinsic from extrinsic duodenal lesions and to localize the lesion for the surgeon.

Treatment

Division of the annular ring may cause pancreatic and duodenal fistulae and pancreatitis and may fail to relieve the obstruction. Bypass is the procedure of choice in infants and adults and has the highest cure rate and the least morbidity and mortality. The procedure of choice is a gastrojejunostomy with or without gastric resection.[9,10]

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IMPORTANT INFORMATION: *This is a Schedule V substance by Federal law; diphenoxylate HCl is chemically related to meperidine. In case of overdosage or individual hypersensitivity, reactions similar to those after meperidine or morphine overdosage may occur; treatment is similar to that for maperidine or morphine intoxication (prolonged and careful monitoring). Respiratory depression may recur in spite of an initial response to Nalline® (nalorphine HCl) or may be evidenced as late as 30 hours after ingestion. LOMOTIL IS NOT AN INNOCUOUS DRUG AND DOSAGE RECOMMENDATIONS SHOULD BE STRICTLY ADHERED TO, ESPECIALLY IN CHILDREN. THIS MEDICATION SHOULD BE KEPT OUT OF REACH OF CHILDREN.*

Indications: Lomotil is effective as adjunctive therapy in the management of diarrhea.

Contraindications: In children less than 2 years, due to the decreased safety margin in younger age groups, and in patients who are jaundiced or hypersensitive to diphenoxylate HCl or atropine.

Warnings: Use with caution in young children, because of variable response, and with extreme caution in patients with cirrhosis and other advanced hepatic disease or abnormal liver function tests, because of possible hepatic coma. Diphenoxylate HCl may potentiate the action of barbiturates, tranquilizers and alcohol. In theory, the concurrent use with monoamine oxidase inhibitors could precipitate hypertensive crisis.

Usage in pregnancy: Weigh the potential benefits against possible risks before using during pregnancy, lactation or in women of childbearing age. Diphenoxylate HCl and atropine are secreted in the breast milk of nursing mothers.

Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria and paralytic ileus.

Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils, tachycardia and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. Use a narcotic antagonist in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. *Liquid,* 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

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When diarrhea has his number...



Lomotil puts him back in the game.

Physicians and patients both want prompt control of the symptoms of diarrhea. A rapid, uncontrolled loss of fluids and electrolytes can cause a medical crisis, particularly in children, and in patients who are seriously ill, or in people who are badly undernourished.

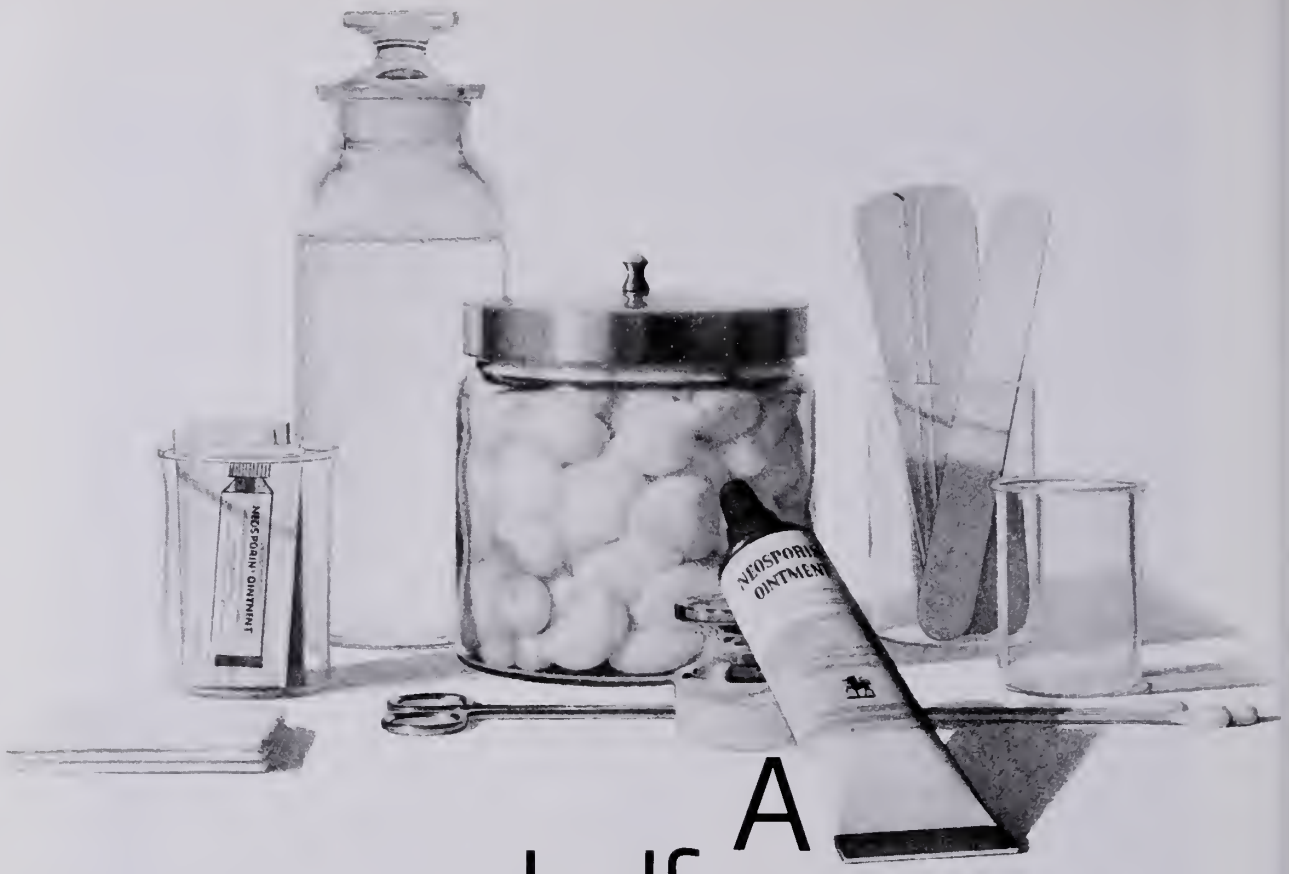
Lomotil usually stops diarrhea promptly. This rapid action halts the emergency aspect of diarrhea and is comforting and reassuring to the patient. Electrolyte and fluid losses can be corrected while the specific cause of the diarrhea is being determined. If an infective agent is the cause, appropriate antibiotic therapy should be given along with Lomotil.

Lomotil has few side effects, and those that do occur are generally mild.

Lomotil®
TABLETS/LIQUID

Each tablet and each 5 ml. of liquid contain:
diphenoxylate hydrochloride ..... 2.5 mg.
(Warning: May be habit forming)
atropine sulfate ..... 0.025 mg.

Usually stops diarrhea promptly.



A half-ounce of prevention

Use it to prevent a topical infection. Or to treat one that's already started. In either case, it's good medicine. Whether for lacerations, burns, open wounds, IV catheter or surgical aftercare. Neosporin® Ointment provides broad antibacterial coverage against common susceptible pathogens. And since it contains three antibiotics that are rarely used systemically, the risk of sensitization is reduced. Neosporin Ointment. A half-ounce of prevention. Also available in a full ounce of prevention and in convenient foil packets.

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Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs.
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INDICATIONS: *Therapeutically,* used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. WM

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Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

Indications: Edema associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. Also, mild to moderate hypertension.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

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Each capsule contains 50 mg. of Dyrenium® (brand of triamterene) and 25 mg. of hydrochlorothiazide.

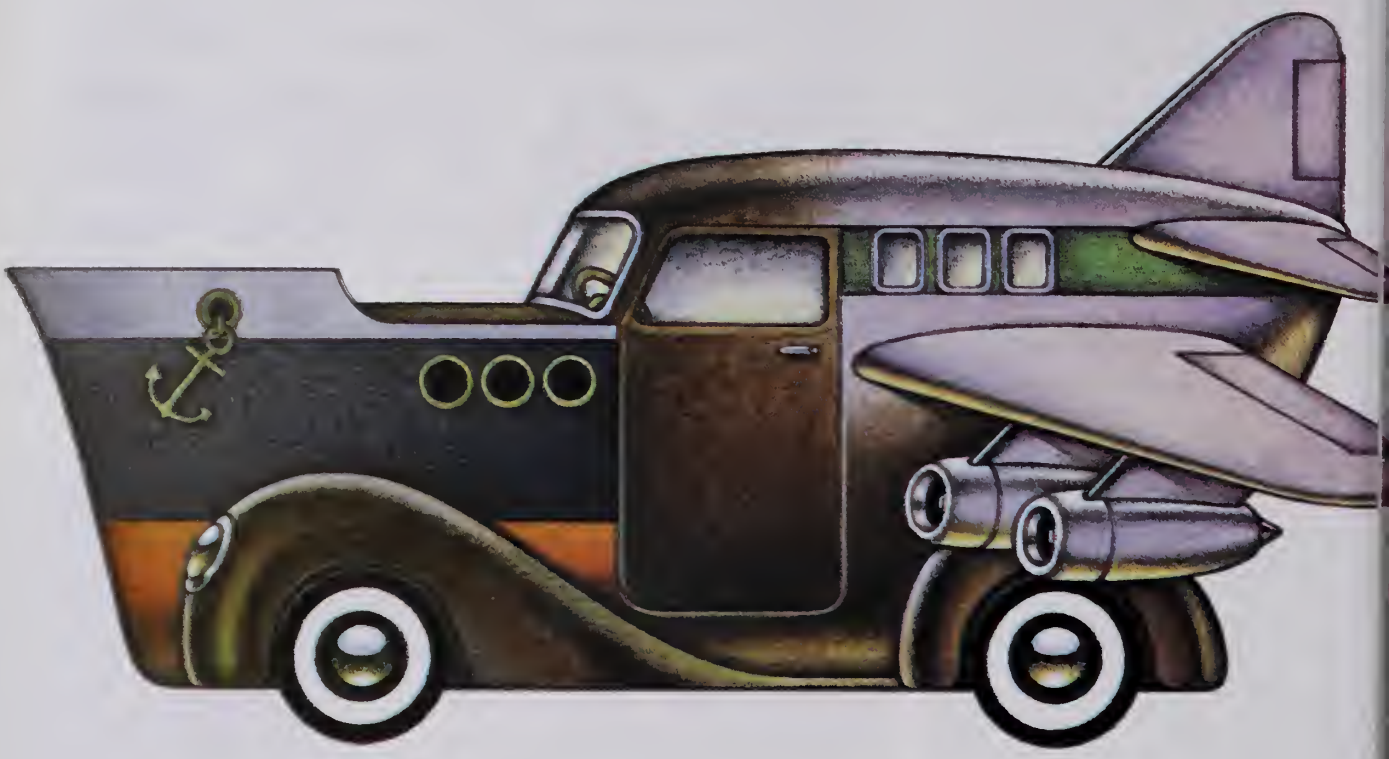
Neither inconvenient potassium supplements nor special K^+ rich diets needed as a rule. Just 'Dyazide' once or twice daily for maintenance.



Two prime reasons patients drop out of hypertensive therapy are (1) the patient failed to understand directions, and (2) the regimen was overly complicated. Dosage is simple with 'Dyazide', easily understood, once or twice daily, depending on response. There's no need to complicate the regimen with potassium supplements or unwieldy potassium-rich diets.

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Dosage: 25 to 50 mg. 1 hour before travel.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS. Administration of Antivert during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caus cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals wh have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occ with use of this drug, patients should be warned of this po sibility and cautioned against driving a car or operati dangerous machinery.

Usage in Children: Clinical studies establishing safety a effectiveness in children have not been done; therefo usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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Antivert®/25 Chewable Tablets
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Editorials

Retroperitoneal Hemangiopericytoma

THE RARE PROBLEM of management of the hemangiopericytoma was reviewed by Bess and Liner* and another case was added to the literature reaffirming the malignant potential of the tumor.* Backwinkel and Diddams estimated an overall 50% lifetime recurrence rate in all of these tumors treated from their review of the literature.[1] Battifora noted a possible increase in metastatic potential in the tumors with the best differentiated pericytes. He also suggested a possible common histogenesis for the hemangiopericytoma, and the hemangioendothelioma (angiosarcoma) with the clinical expression depending on the relative proportions and maturity of the two principal cell constituents.[2] Despite these observations, there exists no real good prognostic indicator for the individual case. Actinomycin D, methotrexate and cyclophosphamide failed to control the tumor in this case report. The experience with high dose methotrexate and citrovorum rescue as an adjuvant after surgical management of the primary has been encouraging in other soft tissue sarcomas. Other therapeutic possibilities include Adriamycin and Imidazole carboxamide which have not been individually reported against this tumor. Radiation does not have a good track record in controling this tumor, but a combination of these modalities seems warranted.

The possibility of chemical exposure producing these tumors is intriguing. The association of polyvinylchloride and angiosarcoma was discovered really by virtue of its rarity. Other compounds such as ethylhydrazine hydrochloride are capable of provoking vascular sarcomas in animals which sometimes resemble the hemangiopericytoma.[3] In vinylchloride exposure there is also a background of hepatic fibrosis which resembles chronic arsenic poisoning.[4] Perhaps an exhaustive exposure history plus a liver biopsy would allow us to discern an association of other vascular sarcomas with some avoidable environmental factor.

John J. Hill, M.D.
St. Louis Park Medical Center

*See page 236.

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Hennepin County Medical Center Grand Rounds

With this issue of Minnesota Medicine,* the Hennepin County Medical Center (formerly Hennepin County General Hospital) will institute what we hope will become a regularly featured Department of the Journal, that is, the Hennepin County Medical Center, Department of Medicine, Medical Grand Rounds. Our first-year Medical Residents will prepare these reviews. They are formally presented at our Department of Medicine Medical Grand Rounds on the third Friday of each month as part of our daily Noon Conference schedule. A luncheon is served, and all are welcome.

Most of our General Medicine Conferences are given by full-time attending staff and their trainees. However, we believe that the busy first-year Resident ought to be given a chance to have a creative educational experience and "pull together" the salient features of an Internal Medicine topic that *interests* the Resident. Most topics picked are of general medical interest. They are not meant to be exhaustive reviews. The Medical Residents have been concentrating their efforts particularly upon pathogenesis, and they tend to seek out controversies and are less concerned with textbook-type presentation of material. They strive to organize from the literature a broad (and current) conceptual approach to their topic, whether it is relatively uncommon, specialty-oriented disease, or a certain aspect of a common disease. Several of our Residents have made use of our excellent medical records system and have finished their presentations by relating a recent practical experience to their topic.

Although certainly biased in their behalf, I believe our residents have produced what they sense as the right combination of an academic and practical approach to a problem. They are assisted by a competent expert in the field, usually one of our full-time attending staff, and myself. For those of you who desire to attend, the formal presentation is limited to 30 minutes, after which a lively discussion is instituted between the presenter, staff, house staff, and students.

One of the motivations the resident has to choose a topic is to call upon his or her experience with a patient with an interesting problem, either on the broad Medical Services or one of the specialties. Presentations of "Heat Stroke," "Gonococcemia," and "Hemolytic-Uremic Syndrome" are some examples of this. The topic of "Heat Stroke" also serves as an example which was called upon frequently by many of our Staff as a useful, practical reference towards the delivery of patient care during our "hot spell" last summer.

Finally, although these reports are not original works in the sense of a composer of music, they are creative, individual, educational efforts analagous to an orchestrator of music, produced during the very busy first year of the trainee's residency. I believe that the knowledge contained and the style of delivery will be useful and enjoyable to the readership.

Arthur Leonard, M.D.
Hennepin County Medical Center

*See page 263.

Harold A. Diehl Award

The committee for the Diehl Award given annually by the Minnesota Medical Alumni Association solicits nominations for this award from the physicians of Minnesota. The award is presented to one or more physicians meeting these four major criteria:

1. Preferably an alumnus of the University of Minnesota Medical School.
2. Not engaged in an academic capacity.
3. Has made outstanding contributions to the Medical School, the University, the Alumni Association or the community at large.
4. Have a relatively long experience in the field of medical science or a related field.

Nominations for the 1975 awards should be sent by 1 May 1975 to:

Konald A. Prem, M.D.
Chairman, Diehl Award
Box 395
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Hearing Aids

THE CONSERVATION OF HEARING Committee of the Medical Association joins with the Academy of Ophthalmology and Otolaryngology and the Minnesota Speech and Hearing Association to encourage your close reading of the article, "Hearing Aids: Help for Many Hearing-Impaired Persons."* Over the past few years, there has been more and more information in the popular press about hearing loss and its causes (e.g., noise) and its treatment (e.g., acupuncture, and, more realistically, amplification). Patients are asking us many questions based upon information they have read or misread, and it is important to be up to date and realistic about what is available for them. Much of the publicity has been about problems associated with the purchase of hearing aids. One effect has been the passage of legislation that begins the job of protecting the hearing aid consumer. Physicians have been given a significant role by this legislation in identifying problems amenable to medicine or surgery before the hearing aid is tried and in advising patients about the need for a hearing aid trial or for audiologic consultation. The article provides helpful information to assist you in your response to patient questions.

In August of 1973, a law went into effect in Minnesota which prohibits a hearing aid from being sold to a new hearing aid consumer under the age of 18 and over the age of 60 without the recommendations of a physician or audiologist. These age groups were specifically chosen because the pediatric and geriatric hearing impairment must be considered with utmost respect and consideration. The law implies certain responsibilities for the clinician who makes the hearing aid recommendation. After any medically or surgically amenable pathology is ruled out, the presence and amount of hearing loss must be determined. Relying on hearing tests not produced under the supervision of a physician or audiologist is fraught with the possibility of an inappropriate conclusion. The final determination that must be made is whether or not a hearing aid might be of benefit. The "proof is in the pudding". A trial before purchase is a wise recommendation.

The incidence of hearing loss will continue to rise as more people live longer. The vast majority of hearing-impaired persons can enjoy at least some degree of rehabilitation, and for most of them the primary means is the use of a hearing aid. We must be prepared to direct the hearing-impaired patient to the appropriate resources.

Arndt J. Duvall, III, M.D.
Chairman
Committee on Conservation of Hearing
Minnesota State Medical Association

*See page 269.

Light Microscopy of Glomerular Diseases

FOR THE CLINICIAN and morphologist interested in renal disease Dr. Abe Fox's excellent paper, "Light Microscopy of Glomerular Disease"* with its precise descriptions, beautiful and sharp illustrations, and clearly defined terms is a necessary adjunct to understanding and diagnosis. There has long been a need for a compact yet thorough presentation of the morphologic basis of renal glomerular disease in terms of clinical application and Fox has filled just such a need in his paper. He demonstrates convincingly how much information can be learned from light microscopy alone and for those in the majority for whom electron microscopy and/or fluorescence microscopy are not available, this information is of great value. He also defines the instances in which these special areas of study, particularly immunofluorescence, are essential for diagnosis. His unique and provocative descriptive classification of renal glomerular disease and how it relates to clinical renal disease should be of interest to all.

Barbara A. Burke, M.D.†
Minneapolis, Minnesota

*January issue, MINNESOTA MEDICINE, page 69, 1975.

†Associate Professor of Laboratory Medicine and Pathology, University of Minnesota School of Medicine, Minneapolis, Minnesota.

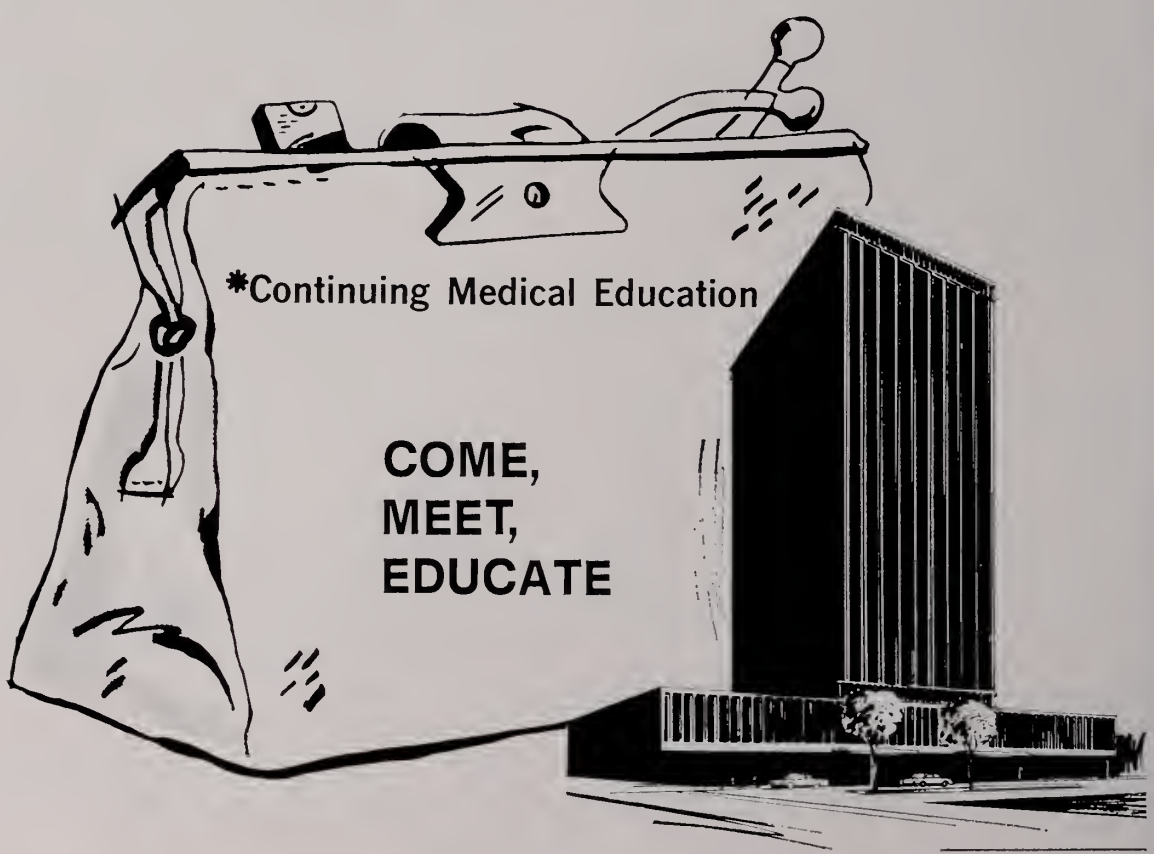
Annual Meeting

The Minnesota State Medical Association's Annual meeting in St. Paul, May 21-23, 1975, at the St. Paul Hilton Hotel.

MINNESOTA STATE MEDICAL ASSOCIATION

122nd Annual Meeting

CME*



MAY 22, 23, 1975 ST. PAUL HILTON HOTEL



Putting out the fires of arthritic pain

Rheumatoid arthritis can sometimes spread like wildfire, with joint after joint going up inflamed: "The usual onset is manifested by spotty joint involvement but an acute onset of symmetrical polyarthritis may be noted."*

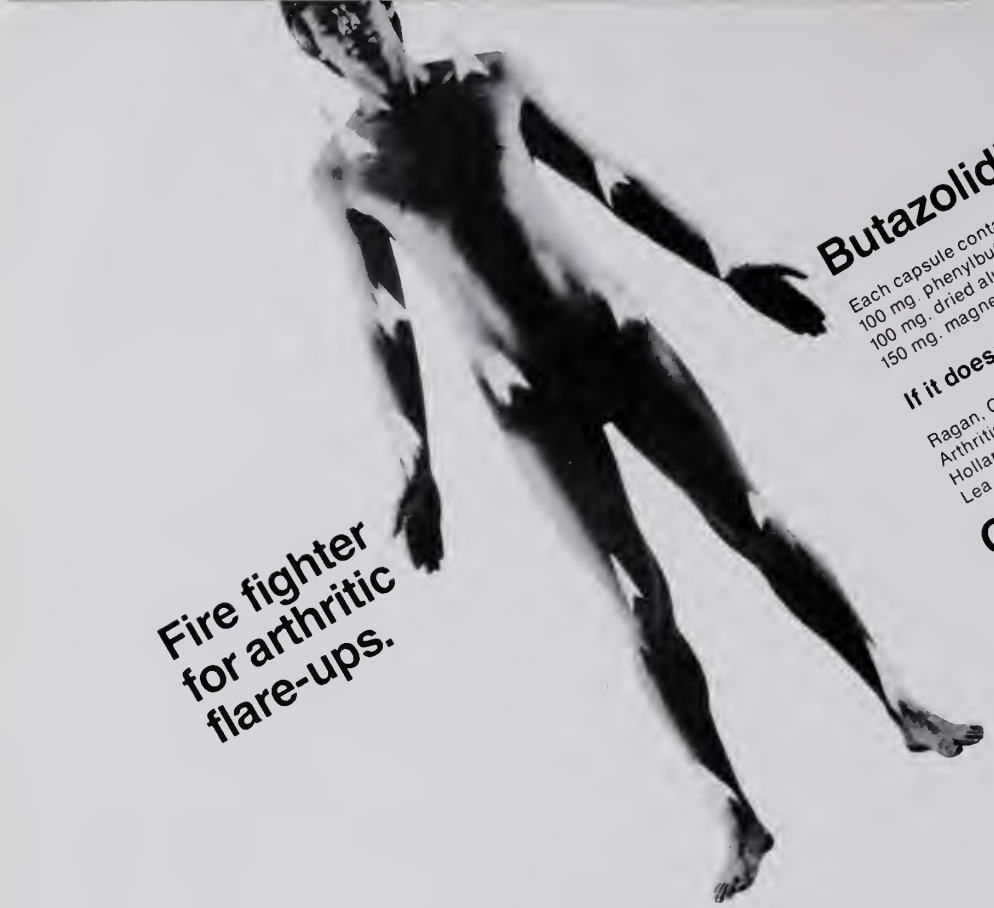
If aspirin fails, consider Butazolidin alka. Giving one capsule four times a day often provides prompt, pain-relieving, anti-inflammatory action to help restore joint mobility. The results you get within a week can be maintained on as little as one or two capsules daily.

Serious side effects can occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings, contraindications and adverse reactions. For full details, please read the prescribing information. It's summarized on the back of this page.

Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.



Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.

Ragan, C.: The Clinical Picture of Rheumatoid Arthritis, in Arthritis, ed. 8, edited by J. L. Hollander and D. J. McCarty, Jr., Philadelphia, Lea & Febiger, 1972, chap. 21, p. 335.

Geigy

Fire fighter for arthritic flare-ups.

Important Note: This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Substitute alka capsules for tablets if dyspeptic symptoms occur. Patients should discontinue the drug and report immediately any sign of: fever, sore throat, oral lesions (symptoms of blood dyscrasia); dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.
Indications: Rheumatoid arthritis, osteoarthritis, bursitis, acute gouty arthritis and rheumatoid spondylitis.
Contraindications: Children 14 years or less; senile patients, history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia; history or presence of drug allergy; blood dyscrasias; renal, hepatic or cardiac dysfunction; hypertension; thyroid disease; systemic edema; stomatitis and salivary gland enlargement due to the drug; polymyalgia rheumatica and temporal arteritis; patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.
Warnings: Age, weight, dosage, duration of therapy, existance of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid) Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.
Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight; complete weekly (especially for the aging) or an every two week blood check, pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
Adverse Reactions: This is a potent drug, its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia, ulcerative stomatitis, salivary gland enlargement.
(B)98-146-070-J (10/71)

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Grand Rounds

Hemochromatosis

CONRAD LUNDBLAD, M.D.*

DISEASES OF IRON storage encompass a spectrum of disorders, the classic example of which is idiopathic hemochromatosis. In this entity, massive iron accumulation is associated pathologically with widespread hemosiderin deposition and fibrosis, and clinically with liver cirrhosis, skin pigmentation, diabetes, and cardiac failure. Most people feel that this form of iron overload is genetic in origin. However, lesser degrees of iron overload and organ dysfunction, commonly termed "hemosiderosis," may have a variety of etiologies and are considered "acquired." Differentiation clinically along this spectrum may be difficult, but is important in treatment.

Historically,[1] Trousseau in 1865 first associated cirrhosis, diabetes, and skin pigmentation. Shortly thereafter, tissue iron deposition was associated with the clinical syndrome. Trosier in 1871 termed the disease "pigmentary cirrhosis in sugar diabetes," and later "bronze diabetes." In 1889 Von Recklinghausen introduced the term "hemochromatosis." In 1935 Sheldon postulated that idiopathic hemochromatosis is caused by an inborn error of metabolism. Since that time, several investigators have uncovered various degrees and types of iron overload, with variable clinical expression. An exact genetic defect has never been defined; and one prominent investigator, MacDonald,[2] believes there is none—he considers all cases acquired.

Fully-expressed hemochromatosis is not common; but, unfortunately, it is usually a postmortem diagnosis. As will be seen later, patients with this disease have been seen at Hennepin County Medical Center, but almost always hemochromatosis has been surprise autopsy diagnoses. Published reports have indicated autopsy incidences of one in 7,000[3] and one in 800,[4] and clinical incidences of one in 6,200[5] and 9.5 in 100,000[6] hospital admissions.

*Medical Resident, Hennepin County Medical Center, Minneapolis, Minnesota. Posthumous.

Edited by: Arthur Leonard, M.D., Coordinator, Medical Education and Attending Physician, Department of Medicine, Hennepin County Medical Center.

Iron Metabolism

Basic to an understanding of iron overload disorders is a brief consideration of iron metabolism. Total body iron in the adult is 3-5 grams. Two-thirds of this is in hemoglobin; one-fifth is in iron stores as hemosiderin and ferritin, primarily in the liver, spleen, and bone marrow; and the remainder is in myoglobin, enzymes, and transferrin.[7] Transferrin is the transport globulin for iron. The adult daily iron requirement for males is 1-2 mg., which is the amount of daily loss by desquamation of epithelial cells from the gastrointestinal tract and skin.[8] Since about 20% of ingested iron is usually absorbed, a dietary intake of about 10 mg. daily is required.[9] Normally, absorption of iron is sensitive to total body stores by mechanisms which are still not completely defined. Previous attention has been directed to a concept of intestinal mucosal "block"—i.e. the amount of ferritin in mucosal cells determining the rate of iron absorption—but this concept has since been invalidated.[7] However, the intestine does seem to play some incompletely defined role, as does total body iron stores and rate of erythropoiesis.[7] Iron absorption correlates closely with the amount of iron administered at all dose levels up to that which causes death from acute iron poisoning.[7] Some kinetic studies of iron absorption suggest an enzymatic process or carrier mechanism for intestinal modulation of iron absorption, irrespective of ferritin.[7]

Dietary iron is in two forms—ionizable and heme (porphyrin) iron. Gastric juices form complexed and ionized iron which are then soluble (ferrous greater than ferric) when neutralized in the small intestine, where they are absorbed. Heme iron is split from porphyrin molecules in small intestinal epithelial cells, possibly by xanthine oxidase and heme oxidase. Iron is then transferred to plasma as transferrin, then distributed according to body needs. Absorption and transfer of iron is maximal in the duodenum, less in the jejunum and ileum.[10] Unwanted iron is deposited

as ferritin and hemosiderin, generally in the reticuloendothelial system. Hemosiderin may be a complex aggregate of ferritin molecules, formed when the iron load exceeds a critical level.[7]

There is essentially no active iron excretion.[9] The gastrointestinal tract eliminates unabsorbed intake, but actively excretes only a small amount of iron by desquamation. The skin also desquamates small amounts. The kidney excretes essentially no iron, and the bile a small amount which is mostly reabsorbed by the intestine. Male adults lose about 1 mg. of iron daily, and menstrating females lose 25-100 mg. with each menses.[9]

Etiology

Compared to normal body stores of 3-5 grams of iron, total iron stores of idiopathic hemochromatosis are in the range of 15-20 grams.[1] Based upon considerations of iron metabolism, there are several possible causes of iron overload disorders including idiopathic hemochromatosis. Mechanisms could include: 1. Excess intake of iron; 2. Increased absorption; 3. Abnormal transport of iron; 4. Abnormal deposition of iron; or 5. Decreased excretion (not significant here).

The first question to consider is whether iron causes tissue damage. Experimental studies in animals have indicated that iron overloading alone does not produce hemochromatosis.[11,12] However, when associated with choline-deficient or folic acid-deficient diets, hemochromatosis could be produced.[11,12] The question is whether these results can be transposed to humans, since manifestations in humans do not occur for 40-60 years and there may be a genetic defect in the handling of iron. Support for the concept that iron does cause tissue damage is found in documented cases of reversal of clinical findings and even biopsy-proven cirrhosis in patients treated by phlebotomy.[8,13]

Excess intake of iron can occur orally through diet, medications, tonics, etc., or parenterally through transfusions. The classic case of dietary iron overload is that of the South African Bantus, who use iron cooking utensils, particularly for their local alcoholic brew.[14] In this population, 70% of adult males, and 25% of adult females have hemosiderosis, with a peak at ages 40-60 years. The hemosiderin deposition in these people occurs primarily in reticuloendothelial organs (liver, spleen, marrow), and less commonly in other organs. However, only 3% develop dysfunction of other organs such as the heart, pancreas, and other endocrine organs, typical of primary or idiopathic hemochromatosis.[14]

Various hematologic disorders may be associated with iron overload and excess deposition of hemosiderin, primarily in reticuloendothelial organs. Increased iron absorption in this context occurs in states of accelerated erythropoiesis and defects in red cell maturation, in response to anemia but with inadequate utilization of iron.[1] Examples are chronic hemolysis, folate deficiency, B^{12} deficiency, pyridoxine-responsive anemia, thalassemia, and sideroblastic anemia.[1] Multiple transfusions in the therapy of refractory anemias may also contribute to iron overload.[1]

As mentioned previously, Sheldon postulated an inborn error of metabolism theory for the etiology of idiopathic hemochromatosis, which has been widely supported but never precisely defined. One possibility is a defect in gastrointestinal uptake of iron at the mucosal cell level, perhaps influenced by a gastric or pancreatic factor.[1] A gastric iron-binding protein called "gastroferrin" has been found which normally binds iron and is absent in patients with hemochromatosis.[15] Another possibility is deficiency of xanthine oxidase, which stimulates release of iron from ferritin, but studies of patients on allopurinol have not shown any significant change in iron stores or absorption.[7] Other possibilities are abnormalities in ferritin or hemosiderin molecules, or defects in the ability of the reticuloendothelial system to remove iron from plasma resulting in accumulation in other tissues.[7] While genetic defect is unknown, familial studies seem to indicate some form of genetic basis for idiopathic hemochromatosis.[16,19]

Not all investigators believe in a genetic theory for the etiology of idiopathic hemochromatosis. Chief proponent of a purely acquired theory is MacDonald, who believes hemosiderosis and hemochromatosis are variants of the same disease, and are caused by hematologic disorders, transfusions, nutritional imbalance, or alcoholic cirrhosis.[2,4,20] He believes hemosiderin deposition is incidental and is the result of, not the cause of, tissue damage from other disorders.[21] Alcoholism is common in hemochromatosis, reports varying from 25-85%.[3,4,7] Alcoholic beverages, particularly cheap wines, contain significant amounts of iron, and hemochromatosis is more common in "winos" and in areas of heavy wine consumption such as Italy and France.[6,22] Significant amounts

of stainable iron in the liver have been found in 58% of normal livers and 80% of cirrhotic livers in studies of unselected autopsies and liver biopsies.[21,23] Hemochromatosis has also been reported to develop following surgical portacaval shunting.[24,25] Iron absorption rates have been studied, and several investigators have found increased absorption in patients with alcoholic cirrhosis and disorders related to alcoholism, such as malnutrition, anemia, and pancreatitis, as well as other types of cirrhosis and hepatitis.[26,29] Nevertheless, the rate of iron absorption and degree of massive iron overload in idiopathic hemochromatosis is unusual in, and not always associated with, alcoholism and related disorders.[1,7,27]

An editorial in LANCET summarizes the opposing views of hereditary versus acquired etiology of hemochromatosis, and supports the conclusions of Sherlock[30]: (1) Familial evidence is overwhelming. (2) The amount of iron in the liver in alcoholic or nutritional cirrhosis is usually not as great as in idiopathic hemochromatosis. (3) Alcoholics are malnourished and absorb increased iron, accentuated by pancreatic insufficiency. Also, patients with idiopathic hemochromatosis are often alcoholics, but this may merely encourage the expression of the genetic defect.

Clinical Features

Clinical features of idiopathic hemochromatosis include liver cirrhosis, diabetes, skin pigmentation, cardiac failure, endocrine dysfunction, and arthropathy. There is also a rare occurrence of acute abdominal crisis with acute pain and shock, usually rapidly fatal, of unknown etiology.[1,7] Organ dysfunction is generally related to massive iron deposition in parenchymal cells in hemochromatosis, as opposed to reticuloendothelial cells in hemosiderosis.[1] Clinical features usually do not appear until middle age (40-60 years), after years of slow accumulation of iron, and males predominate over females 10:1 ratio (related to menses and pregnancies).[5]

The most prominent clinical feature is cirrhosis. This is probably due to the fact that the liver is a major storage depot for iron and the site of transferrin synthesis.[1] Hepatomegaly is the most common finding, often with few other signs of disease.[7] Pathologically, the findings are portal fibrosis or cirrhosis, and hemosiderin deposited in Kupffer cells and heavily in parenchymal cells.[31] Of interest also is the fact that there is an even higher incidence of hepatomas in hemochromatosis than there is in alcoholic cirrhosis for unknown reasons.[4,32]

Diabetes occurs in about 60% of patients with hemochromatosis, and it may be the presenting finding.[33] In those patients with diabetes, a family history of diabetes is more common but not always present, which may explain why not all patients show improvement in their diabetes with phlebotomy therapy.[33] Another factor in the development of diabetes is the liver disease itself. Chronic liver disease has been shown to produce endogenous insulin resistance and hyperinsulinemia.[34] Therefore, family history and liver disease may be factors in the development of diabetes in hemochromatosis, in addition to direct damage to the pancreas by iron deposition.

Skin pigmentation occurs in 90% of patients with hemochromatosis.[35] The characteristic color is slate-gray or bronze,[5] and pigmentation is most prominent in exposed areas of the body.[9] In the past, the pigmentation was thought to be due to hemosiderin in the skin; but later studies have shown it to be due to increased melanin.[35] Hemosiderin is frequently absent in the skin, making skin biopsy generally unhelpful as a diagnostic procedure.[7] The cause of increased melanin is unknown, but factors may include melanocyte injury from iron, epidermal thinning or occasionally adrenal insufficiency.[35]

Another common clinical feature, sometimes considered the fourth component of a classic tetrad of hemochromatosis, is cardiac disease.[1] Finch and Finch found a 31% incidence of fatal cardiac failure in a large series of patients with hemochromatosis.[3] Refractory heart failure is the common finding, and it correlates pathologically with extensive cardiac iron deposits and myocardial fibrosis.[36] Iron deposits occur initially in ventricular myocardium, later in the atria, and less commonly in the conducting system.[36] Arrhythmias are usually supraventricular and correlate with atrial iron deposits, while A-V conduction disturbances and ventricular arrhythmias are less common.[36] Despite the age incidence of hemochromatosis and possible other causes of cardiac disease, heart failure without other demonstrable cause and with improvement following phlebotomy has been described.[36]

Endocrine organs other than the pancreas may

be involved with iron deposition, fibrosis, and resulting clinical dysfunction.[1,7] Adrenal insufficiency, pituitary hypofunction, hypothyroidism, hypoparathyroidism, and gonadal atrophy have all been described, but these clinical findings are rare.[1,5,7] Gonadal atrophy may also be due to the liver disease.[1]

In recent years, a rather characteristic arthropathy has been described in patients with hemochromatosis.[37] In a specific investigation of joints in 32 patients with idiopathic hemochromatosis, 16 had significant arthropathy, characterized as a progressive polyarthritis usually starting in the metacarpophalangeal joints of the fingers.[37] Articular chondrocalcinosis is common, but hemosiderin deposits are not always present.[37]

Diagnosis

The diagnosis of hemochromatosis is often difficult, especially in its earlier stages when all clinical features are not present. Based upon the previous discussion, physical signs and laboratory findings of specific organ dysfunction are most helpful. Particular clues are the presence of hepatomegaly or cirrhosis in combination with other disorders such as diabetes, skin pigmentation, heart failure, or arthropathy. The best screening test is probably the serum iron and total iron binding capacity (which reflects transferrin levels).[1,19] The serum iron is usually greater than 150 micrograms percent, with 70-100% saturation of the iron binding capacity.[7] However, there are pitfalls with this test, as serum iron fluctuates normally and does not always correlate well with total body iron stores; also, transferrin levels may be decreased with lack of liver synthesis, giving low TIBC.[1] Therefore, caution should be exercised with any isolated abnormal test, and clinical correlation is necessary.

Other common tests which are helpful but less specific include liver function tests (which may be normal early), glucose tolerance testing, endocrine function tests, electrocardiograms, joint Xrays (particularly of hands), and hematologic studies (peripheral morphology, hemoglobin, tests for hemolysis and vitamin deficiency, etc.)[1,5,7]

The best test for definitive diagnosis of hemochromatosis is the liver biopsy with stains for iron, ideally with quantitative determination of iron concentration.[5,38] Differentiating features on liver biopsy are as follows: (1) Iron in reticuloendothelial (Kupffer) cells only is found in hemolysis, antecedent hepatitis, and post-transfusion; (2) Iron in equivalent amounts in both Kupffer and parenchymal cells is found in iron overload associated with certain anemias; and (3) Iron heavily and predominantly in parenchymal cells is found in idiopathic hemochromatosis and alcoholic cirrhosis.[31] Portal fibrosis and cirrhosis is the other feature of hemochromatosis, with less tissue damage compared to iron deposition in idiopathic hemochromatosis than in alcoholic cirrhosis.[31] When liver biopsy suggests hemochromatosis, a search for involvement of other organs should be undertaken.[31]

Other biopsy studies are less helpful. Bone marrow iron reflects reticuloendothelial iron and may be selectively increased (with hemolysis, etc.) without increased parenchymal iron in other organs.[1] Skin biopsy is usually not helpful, as pigmentation in hemochromatosis is due to melanin, not hemosiderin.[35] Synovial biopsy often does not show hemosiderin deposits.[37] If gastrointestinal endoscopy is done, iron stains may show mucosal hemosiderin deposits.[5]

Another approach to diagnosis is by urinary iron excretion following administration of iron chelators such as desferrioxamine, but chelators are not approved in the United States for this use.[1,39] The technique of testing involves collecting a baseline 24-hour urine for iron, then another one following intramuscular administration of 500 mg. of desferrioxamine. Greater than 4.0 mg. iron excretion compared to the baseline is diagnostic of iron overload extending beyond the reticuloendothelial system and involving parenchymal cells.[39]

Differential diagnosis usually involves hemochromatosis versus alcoholic cirrhosis associated with other diseases such as diabetes.[7] Other diseases more easily differentiated include primary hematologic disorders, Addison's disease, porphyria cutanea tarda, panhypopituitarism, neoplasm, acanthosis nigricans, argyria, and chronic arsenic poisoning.[7]

Treatment

The treatment of hemochromatosis is removal of iron. Phlebotomy therapy was first tried in 1942, and successfully around 1950.[8] Considering an iron overload of 15-20 grams, it usually takes 10-12 months to deplete iron stores by removing 500 ml. of whole blood (250 mg.

iron) once or twice weekly.[8] Therapy at this frequency is continued until the serum iron falls to below normal and the TIBC increases.[1] Then the frequency of phlebotomy is decreased to a maintenance rate of removal of 4-6 units per year.[8] During therapy, the hemoglobin should be monitored and not be allowed to drop below 11-12 gm.%.[8] With adequate diet, hypoproteinemia is not usually a problem; if it is, the patient's plasma may be reinfused.[8]

The other possible method of removal of iron is with iron chelators such as desferrioxamine (not approved in the United States).[1,40,41] However, chelators remove much smaller amounts of iron (maximal 20-30 mg. per day) than phlebotomy (250 mg. per unit), although they could be useful for treatment of "secondary" hemochromatosis following multiple transfusion for refractory anemia, or other contraindication to phlebotomy.[1,40,41] Use of chelators also involves daily intramuscular injections since they are not effective orally.[1]

In addition to removal of iron, therapy of hemochromatosis, of course, also must include treatment of specific organ dysfunction, such as discontinuance of alcohol, insulin, digitalis, etc.[2,7]

Prognosis

Average survival rate in hemochromatosis following diagnosis was 18 months in 1935, 4.4 years in 1955 (related to use of insulin) and seven years in 1969 (related to phlebotomy).[7] The leading cause of death is liver disease, including variceal bleeding, followed by cardiac failure and rarely now by diabetic complications.[7] There are documented cases of reversal of clinical findings with phlebotomy therapy.[1,8,13] An important factor in future prognosis may be earlier diagnosis by investigation and prophylactic phlebotomy of relatives of patients with advanced idiopathic hemochromatosis.[5,8]

Review of Cases at Hennepin County Medical Center

In the eight-year period of 1965-1972, there have been 3,145 autopsies performed at this hospital. A diagnosis of hemochromatosis has been made in three cases. In none of these cases was the diagnosis considered pre-mortem, except in one a few days before death. This patient was a 64-year-old alcoholic female with hepatomegaly, portal cirrhosis, and skin pigmentation with no history of anemia, iron therapy, or diabetes. Serum iron was 156, but with only 47% iron saturation. Liver biopsy showed marked hemosiderosis, and skin biopsy was nondiagnostic. Autopsy showed extensive iron deposition in the liver, spleen, pancreas, adrenals, and myocardium.

The other two cases of hemochromatosis were in males, ages 60 and 79 years. One had cirrhosis, heart failure, and skin pigmentation; but he also had B_{12} deficiency, post-gastrectomy and several normal serum irons with low TIBC and normal saturation. Liver biopsy was not done. The other patient had no serum irons or binding capacities. Liver biopsy two years previously showed cirrhosis but no iron stains were done.

In the same eight-year time period, an autopsy diagnosis of increased hemosiderin confined to reticuloendothelial organs was made in 31 cases. The primary disease was alcoholic cirrhosis in 11, hematologic disease and/or transfusions in nine, myxedema one, neoplasm one, chronic active hepatitis one, and miscellaneous eight (including chronic renal failure).

Review of face-sheet diagnoses on hospital admissions from April, 1972, to April, 1973, shows no diagnoses of either hemochromatosis or hemosiderosis. Diagnostic combinations of cirrhosis and diabetes, cirrhosis and heart failure, and all three in combination are noted in nine patients during this time period. All of these patients are alcoholics, and only two are females. One patient has a history of migratory polyarthritis in addition to cirrhosis, diabetes, and chronic congestive heart failure. The only patient in whom the diagnosis of hemochromatosis was considered was a 47-year-old male alcoholic with cirrhosis, heart failure, diabetes, skin pigmentation, and elevated serum iron and iron saturation. He died from hepatic failure and gastrointestinal bleeding, and no autopsy was obtained.

There have been no patients undergoing phlebotomy therapy for hemochromatosis in GI or Hematology Clinics here. A patient was recently diagnosed, but has not returned for follow-up and therapy.

In conclusion, although hemochromatosis is uncommon, it does occur at this hospital. We should at least consider the possibility in our numerous patients with cirrhosis, particularly when associated with diabetes, heart failure, skin pigmentation, endocrinopathy, or arthropathy. Earlier diagnosis can lead to effective therapy by phlebotomy.

Addendum

Dr. Lundblad was Chief Resident at Hennepin County Medical Center. He died as a consequence of a very rapid course of acute monocytic leukemia in January of 1975. It is in his honor that we dedicate this new, regular feature in MINNESOTA MEDICINE, the Hennepin County Medical Center, Department of Medicine Grand Rounds. Because of the suddenness of his illness and his financial situation as a Medical Resident, he was unable to provide optimally for his wife and two infant children. A *Lundblad Family Trust* has been established to, hopefully, allay any economic compromise for his family. Contributions may be directed to: The Lundblad Family Trust, Department of Medicine, Hennepin County Medical Center, Fifth Street and Portland Avenue South, Minneapolis, Minnesota 55415. If you require further information you may contact one of the following physicians at the Department of Medicine, 348-8224; Drs. Thomas Braxtan, Richard Sweet, Thomas Martin, or Alvin Schultz.

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Krishna M. Saxena, M.D.

Dr. Krishna M. Saxena has been elected Chief of Staff of the St. Paul Children's Hospital for 1975. Dr. Saxena succeeds Dr. Robert T. Dooley.

Dr. Saxena joined the Hospital in 1967 and has been serving as Director of Medical Education since 1968. He is an Associate Professor of Pediatrics and Associate Professor of Family Practice at the University of Minnesota.

Special Article

Hearing Aids

Help for Many Hearing-Impaired Persons

WAYNE O. OLSEN, Ph.D.* and KEVIN K. SCHREURS, M.A.*

Contrary to the opinion of many professional workers, many persons with sensori-neural hearing losses can and do benefit from hearing aid use. In fact, the majority of present day hearing-aid wearers are persons having sensori-neural hearing losses. Advantages of trial periods of hearing aid use before purchase are discussed. The importance of providing amplification for hearing-impaired youngsters during their prime time for language learning and development (the first three years of life) is also discussed.

ALTHOUGH CURRENT MEDICAL practice provides treatment and at least partial if not complete correction of hearing deficiencies for many patients with impaired hearing, there are still many more patients from whom neither medication or surgery can restore hearing to a socially usable level. Many persons with sensori-neural hearing losses need the amplification provided by a hearing aid in order to monitor their sound environment and to communicate. This also applies to persons with conductive hearing losses who are not candidates for surgery or do not elect to undergo surgery, and to some with mixed (conductive and sensori-neural) hearing losses who require amplification even after optimal surgical correction.

Misconceptions About Hearing Aids

Many misconceptions exist about who can benefit from the use of a hearing aid and what is expected of a hearing aid. The most common misconception is that persons with sensori-neural hearing losses cannot benefit from hearing aid use.

The reason for this misconception may be that some patients with sensori-neural hearing loss complain that in some situations they can hear the speaker but cannot understand him. Some patients (and some clinicians also) expect too much from a hearing aid. Advertisements on hearing aids promote this with claims that new developments can provide hearing-impaired persons with "natural hearing again." Adverse reports from the patient or from friends and relatives of hearing-impaired persons can lead to the erroneous conclusion that all persons with sensori-neural hearing loss will not benefit from hearing-aid use. The fact of the matter is that the vast majority of present-day hearing-aid users are those with sensori-neural hearing losses.

Other misconceptions are: (1) Persons with unilateral hearing losses are not candidates for hearing-aid use. One innovation in hearing aids places the microphone on the side of the impaired ear but delivers the amplified sound to the other ear. This arrangement results in improved communication for many persons whose unilateral hearing impairment makes listening very difficult in noisy situations. (2) Persons with normal hearing sensitivity for low frequencies (below 1,000 Hz or even 500 Hz) cannot benefit from hearing-aid use. Recent modifications in ear molds have resulted in satisfactory hearing-aid use by persons who have high frequency losses but whose sensitivity for low frequency sounds remains good. (3) Children must be three to four years of age or older before valid decisions can be made about their use of a hearing aid. Hearing aids can be used with benefit even by infants. Failure to provide appropriate amplification for a hearing-impaired youngster during the first two years of life can result in a major delay in the

*Section of Audiology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.

See editorial, page 259.

development of speech and language. It may be impossible later to overcome this delay.

Medical and Rehabilitative Steps in Assisting Hearing-Impaired Persons

Physical Examination

Any person who has hearing difficulties should undergo a physical examination to confirm that the hearing impairment cannot be attributed to some readily treated malady, for example, impacted cerumen blocking the ear canal. The history relative to onset, progression, fluctuations, and accompanying symptoms is necessary to assess the complaint of hearing difficulty and determine its cause. It is important to remember that many hearing problems have multiple etiologies. For example, even though the patient may experience noticeable subjective benefit when a physician removes excess cerumen, there may still remain significant sensori-neural deficit that accounts for most of the hearing difficulty.

Hearing Tests

Hearing tests are critical to determine the degree of hearing loss, to delineate the type of hearing loss (conductive, sensori-neural, or mixed conductive and sensori-neural), and to provide clues that can assist in making a diagnosis. When there is a readily treatable loss, hearing tests are vital in order to assess the extent of impairment prior to treatment, to measure change after treatment, and to suggest other causes. Speech stimuli can provide an estimate of the communicative problems in terms of hearing and understanding speech.

Referrals

Most primary physicians do not see enough patients with hearing problems to warrant the purchase of test equipment, the construction of a quiet test room, or the hiring of the necessary personnel. Family physicians often refer such patients to an otolaryngologist for management of ear problems where hearing tests can be completed routinely as part of the evaluation by a specially trained technician or by a qualified audiologist. Or, the family physician may refer the patient to a local speech and hearing center where an audiologist can complete the necessary audiologic evaluation to provide the additional information needed to assist in the medical diagnosis and to evaluate the communication problems that require attention. Guidance and counseling relative to rehabilitation should be provided by an audiologist. Most importantly, the audiologist can counsel the patient concerning the communicative difficulties that he has experienced or may encounter, and how to cope with them. In addition, the audiologist may recommend and provide or arrange for lessons in speech reading and in auditory training as part of the rehabilitative program. He may discuss with the patient the various amplifiers and devices that are available from the Bell Telephone System to assist in telephone communication (brochures describing such devices are available from the Bell Telephone Company); earphones and other devices are also available to enable the patient to listen more effectively to radio and television. It should be understood that these suggestions may be made with or without a recommendation for hearing-aid use; commonly, a trial period of hearing-aid use is recommended for most patients.

Hearing-Aid Selection

The audiologist may offer a specific recommendation regarding make and model after he has completed various threshold and speech discrimination tests. However, professionally trained audiologists who work in a hearing clinic or who are part of an otologic practice do not sell hearing aids. Rather, they refer the patient to a commercial dealer. The dealer arranges to obtain a properly fitting ear mold for the patient and provides the hearing aid. Some dealers rent the hearing aid to the patient for a trial period; some sell the instrument but provide an explicit warranty that the hearing aid may be returned for full credit (except for the ear mold charge) within a specified period. However, some dealers offer neither of these trial options.

Some audiologists make general recommendations concerning amount of gain, type of ear mold to be used, and so forth, and may provide the patient with a list of reputable dealers. The patient then makes his own arrangements for obtaining a hearing aid.

No matter whether the hearing-aid recommendation is a general one or for a specific make and model, the patient should try the hearing aid for about two weeks or a month before deciding to purchase it. This arrangement is beneficial for two reasons. First, the patient can wear the hearing aid in his everyday environment without any large initial expenditure. Second, the dealer has not made an immediate sale and consequently he

will make a greater effort to satisfy the patient by trying different combinations of hearing-aid adjustments, ear molds and so forth. If, after the trial period, the patient finds that the hearing aid is sufficiently helpful to warrant the expenditure, he can purchase it; if the hearing aid had been rented during the trial period, the rental fee generally applies toward the purchase price. If the patient chooses not to buy a hearing aid, he has not invested a large sum of money for a device he does not find helpful. Many dealers also prefer a trial period arrangement because they find that this arrangement reduces the number of customers who are dissatisfied with the hearing aid and who are irate because they have spent a rather large sum of money for a device that they find useless to them.

In any event, with either the rental or refund arrangement, the hearing aid should be purchased only if the patient finds that the hearing aid is helpful in his family, working, and social environments. Because many dealers provide trial rental or refund arrangements, audiologists are wary of dealers who refuse to make such arrangements and may advise the patient to be equally wary.*

Pediatric Hearing Problems

A few comments should be made about the handicaps encountered by children with impaired hearing. The child with impaired hearing should be identified as early as possible. The concern is not communicative rehabilitation but communicative habilitation. The prime time for language learning and development is during the first three years of life and the auditory channel is the major source of input for learning language and for developing speech. Therefore, early identification of a hearing deficit is vital to language and speech development. A team approach involving the pediatrician (or family physician), otolaryngologist, and audiologist is vital for the assessment of the type and degree of hearing loss, cause of loss, and course of action for the optimal communicative habilitation and ultimate school placement and education of the child. The critical issue here is that the preschool years must not be wasted if the hearing-impaired youngster is to attain his optimal language skills and educational achievement.

The child who has a severe hearing loss often is suspected of having such a loss in early infancy because of his failure to react or respond to normal sounds. This concern should lead to a medical and audiologic consultation and a program of thorough evaluations and necessary habilitation. Unfortunately, the child with a less severe hearing impairment or the one with good hearing for low frequencies (through 250 or 500 Hz) but impaired hearing for the middle and high frequencies causes the greatest confusion for his parents, pediatrician and family physician. These children respond inconsistently to sounds (depending on the amplitude and frequency of the sound) and often are not identified as having hearing losses until they have reached school age. Even a mild hearing loss involving only the higher frequencies (2,000 Hz and higher) can seriously affect early language and speech development. Identification of the hearing difficulty, and the consequent language and speech handicaps at school age result in greater language or educational problems than if the problem is detected earlier and followed by appropriate habilitative measures.

For many hearing-impaired children, a hearing aid is needed for their optimal language learning, progress through formal education, and communication with parents, teachers, and peers. The importance of a careful audiologic evaluation of a child suspected of having a hearing loss cannot be overemphasized. If a hearing loss is found, prompt medical care can sometimes restore hearing. If the hearing loss is not medically treatable, then the assistance of the audiologist in arranging appropriate habilitative and educational programs is most important.

Summary

Current medical practice provides the treatment and correction of many hearing impairments. However, there are many more patients for whom neither medication nor surgery can restore hearing to a socially useful level. Contrary to the opinion of some professional workers, many persons with sensori-neural hearing losses can benefit from hearing-aid use. Medical and rehabilitative steps can be taken to assist the hearing-impaired patient in dealing with his hearing problems; these include trial rental of hearing aids. Although a hearing aid cannot solve all the hearing problems of hearing-impaired children or adults, wearable amplification often is needed for them to monitor their auditory environment and to communicate.

*The Better Business Bureau has prepared a useful brochure on this topic entitled, "Facts About Hearing Aids," which provides useful information for professional workers as well as the public at large. Copies may be obtained from the Council of Better Business Bureaus Inc., 1150 17th Street Northwest, Washington, D.C., 20036. Publication No. 03-0250-73 A 250-873.

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Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or p vent sequelae (rheumatic fever, glomerulonephr of such infections. Deaths from hypersensitivity re tions, agranulocytosis, aplastic anemia and other bl dyscrasias have been reported and early clinical signs (s throat, fever, pallor, purpura or jaundice) may indicate seri blood disorders. Frequent CBC and urinalysis with microsc examination are recommended during sulfonamide therapy. Ins cient data on children under six with chronic renal disease.

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ı, hypoprothrombinemia and methemoglobinemia); *allergic :tions* (erythema multiforme, skin eruptions, epidermal necroly- urticaria, serum sickness, pruritus, exfoliative dermatitis, ana- actoid reactions, periorbital edema, conjunctival and scleral :tion, photosensitization, arthralgia and allergic myocarditis); *rointestinal reactions* (nausea, emesis, abdominal pains, hepa- diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* ıdache, peripheral neuritis, mental depression, convulsions, ia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous :tions* (drug fever, chills, toxic nephrosis with oliguria and ria, periarteritis nodosa and L.E. phenomenon). Due to certain mical similarities with some goitrogens, diuretics (acetazola- e, thiazides) and oral hypoglycemic agents, sulfonamides have sed rare instances of goiter production, diuresis and hypogly- ia as well as thyroid malignancies in rats following long-term inistration. Cross-sensitivity with these agents may exist.

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Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

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Laboratory Letter

Position Paper

Let us make my position perfectly clear.

It is this: The lower limit of normal for total protein, albumin, calcium, cholesterol, and PBI is lower in the supine than the erect position.

If this stance is correct, then lower limits of normal for hospital patients must be lower than in office patients.

After all, patients *walk* into the office before their blood is drawn. But when patients enter the hospital for elective procedures, they usually arrive in the afternoon, *stay in bed* until morning, and *then* have their blood drawn.

Two recent studies indicate the erect or supine position does make a difference.

Study I

In the first study, Doctor Russell Hobbie and I used a computer to calculate normal ranges for 3,389 office patients and 863 hospital patients (We have described the statistical method we employed in a previous paper[1]). Here are highlights of our findings for men (women had the same trends):

TABLE 1

Differences in Lower Limits of SMA-12/60 Tests in Office Versus Hospital Patients

	Calcium			Total Protein			Albumin			Cholesterol		
Age	Off.	Hosp.	Diff.	Off.	Hosp.	Diff.	Off.	Hosp.	Diff.	Off.	Hosp.	Diff.
20	9.0	8.6	−0.4	6.2	5.7	−0.5	3.7	3.5	−0.2	110	105	− 5
30	9.0	8.5	−0.5	6.2	5.7	−0.5	3.7	3.5	−0.2	120	113	− 7
40	8.9	8.4	−0.5	6.2	5.7	−0.5	3.7	3.3	−0.4	130	121	− 9
50	8.8	8.3	−0.5	6.1	5.7	−0.4	3.6	3.1	−0.5	140	121	−19
60	8.7	8.2	−0.5	6.1	5.5	−0.6	3.5	3.1	−0.4	139	113	−26
70	8.6	8.1	−0.5	6.0	5.4	−0.6	3.4	2.8	−0.6	127	104	−23
80	8.5	8.0	−0.5	6.0	5.3	−0.7	3.2	2.7	−0.5	116	96	−20
90	8.3	7.9	−0.4	5.8	5.1	−0.7	3.1	2.5	−0.6	104	88	−16
100	8.2	7.8	−0.4	5.6	4.9	−0.7	3.0	2.4	−0.6	92	80	−12

As you can plainly see, the evidence is overwhelming. In every age group for every test, hospital patients have lower lower limits than comparable office patients.

You could argue that this lower limit phenomona is statistical happenstance—a freak of chance.

That's unlikely.

Or you could say that hospital patients are sicker than office patients. After all, chronic disease lowers values for cholesterol, proteins, and with proteins, calcium and PBI fall since both happen to be bound to protein.

That line of reasoning would be hard to counter unless you had a healthy 25-year-old medical student who offered himself as a volunteer for multiple venipunctures.

Study II

A few months ago, Al Henderson, then a medical student at the University of Minnesota and husband of one of our technologists, offered to undergo a venipuncture every four hours for a week. Then his plan was to jet to Europe, have blood drawn over the mid-Atlantic, then be punctured again after landing in the Netherlands. He wanted to study circadian rhythms—that internal "biological clock" that controls body functions such as temperature, behavior, excretion, and serum levels of various substances.[2,3]

Would we be interested in using our chemical analyzers to perform this test to help him in his study? We would indeed.

We present here only a fragment of the data to illuminate our position.

As you look at the results, remember they represent serum levels of a healthy man at different times of the day and night.

TABLE 2

Differences in Lower Limits* of SMA/12/60 During Different Times of Day and Night

	11 AM	9.1	6.9	3.9	169	4.8
	3 PM	8.8	6.7	4.0	166	4.8
ERECT	7 PM	8.9	7.1	4.1	177	5.0
	11 PM	8.6	6.8	4.0	168	5.0
	3 AM	8.2	6.2	3.8	155	4.1
SUPINE	7 AM	8.3	6.3	3.7	150	4.1
Differences between average values of erect minus supine position		−0.6	−0.6	−0.25	−18	−0.8

*Lower limits calculated as mean values minus 2 Standard Deviations for five results at each of indicated times.

Again the evidence is unmistakable: the supine position lowers the lower limit of calcium total protein, albumin, and cholesterol. PBI, being bound to protein, declines too.

The reason for these declines? Because posture rapidly changes serum protein concentration. When a patient stands, hydrostatic pressure forces protein-poor fluid out of the vascular tree; when he lies down, the fluid returns, diluting intravascular fluid and reducing concentrations of proteins, albumin, calcium, PBI, cholesterol, and hemoglobin and hematocrit as well.[4-7]

These events occur naturally.

That's our position anyway.

Richard L. Reece, M.D.
Editor-in-Chief

Acknowledgments

We thank Al Henderson for donating his blood on 31 occasions and his wife, Clara, for drawing the specimens at 3 a.m. and 7 a.m.

Editor's Note: Because I have become Editor, this will be the last "Laboratory Letter" I shall write. Hereafter Dr. Charles Jarvis will serve as editor of this section which will appear under the heading of "Laboratory Medicine."

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Minnesota State Medical Association Annual Meeting

COME

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EDUCATE

An Invitation to Come . . .

If we told you that CME is required for MSMA membership and you could earn up to 13 credits at the Annual Meeting—would you come? If we told you Dr. Elisabeth Kubler-Ross heads the roster of exciting guest speakers—would you come? If we told you a most interesting, challenging, 100% accredited scientific program is planned for you—would you come? Still undecided? Well, if we told you a "Bavarian Beer Seminar," complete with beer and bratwurst, German band and dancing, souvenir beer steins and more is planned for those attending the Meeting—would you come?

Now that you've decided to come to the 1975 Annual Meeting, you'll want to know what's being served at this once-a-year "scientific smorgasbord." If you prefer seminars, you can choose from a selection that will satisfy the most scrutinizing educational appetites: Infectious Diseases, Cancer, Proctology, Pulmonary Functions, PSRO, Dermatology, Orthopaedics, Ophthalmology, Human Sexuality. To intensify the learning sessions and promote indepth discussion, each seminar will be limited to 100 or less attendance. Members wanting to take part in limited group seminars must pre-register for them. So, when your Annual Meeting registration material arrives, choose the seminars you want to attend and return the forms to the MSMA office as soon as possible. Because of the restricted attendance, seminar registration will operate on a first come-first served basis.

If your tastes in medicine are not covered by seminar subject matter, you may want to sample the general sessions. They provide still more variety on the scientific menu with programs on Immunology, Rheumatoid Diseases, Pain, the Dying Patient, and Surgical Infections. Regardless of your program choices, you'll be pleased to know that the entire educational bill of fare is accredited by the AMA, the AAFP and worth up to 13 credit hours in Category I of the Physicians' Recognition Award!

After the scientific session on Thursday, you are invited to join the festivities at the President's Reception and Annual Banquet. The Minnesota State Medical Association's President, Dr. Barnard Hall and his lovely wife will be at the reception to personally welcome you. The convivial atmosphere of the reception makes it the perfect place to visit with members from all around the state and after the Reception, an exciting program of awards and special citations promises to make the Banquet a most enjoyable way to spend an evening. Distinguished guests from Minnesota and surrounding states will be there, too. And, special honors will be bestowed on members of the Fifty Club for their half century dedication to the practice of medicine. Other awards, including the Distinguished Service Award (which is kept a secret until its presentation),

will also be presented to outstanding members of the Association. You'll want to share in this special occasion where members have the opportunity to honor their colleagues for their outstanding contributions to the medical community. It's a special evening of events that I know each of you will enjoy.

What better way to digest the scientific sessions than with an invigorating game of golf or tennis? So, for all of you Arnold Palmers and Arthur Ashes, we've scheduled golf and tennis tournaments. The White Bear Yacht Club is just a few good drives and a chip shot away from meeting headquarters. If you're bringing your clubs to the Meeting, look forward to a challenging round on this fine championship course. And, if your bringing your tennis racquet, you'll be heading up river to the Lilydale Tennis Club for the MSMA sponsored tennis tournament. The Lilydale courts are tucked snugly away on the Mississippi River bank and allow players to enjoy the unequaled scenery of the Father-of-Waters along with their tennis. Whether or not your ability on the links or court will let you take home a trophy is something only the tournaments can tell. One thing I know you'll be taking home is a lot of great memories of the day.

Something new this year . . . the "Bavarian Beer Seminar." To wrap-up Friday's scientific session, a casual German inspired get-together is planned. Members and their wives, exhibitors, students, everyone who wants to join in the fun is invited to "dine" on bratwurst and kraut served with the traditional stein of beer. A nine-piece German band will be on hand with their Bavarian brand of toe-tapping, polka style music. When the scientific work is over on Friday, I hope you stick around for the "brats and brew" fest. And, when the toasting is over, you can take your empty stein home with you as a remembrance of MSMA's 122nd Annual Meeting!

I've already dusted off my CME report form and taken my lederhosen out of moth balls. You'll be hearing more about the MEET and EDUCATE portions of our Meeting theme in subsequent issues. For now, I hope you'll accept our cordial invitation to COME to the Minnesota State Medical Association's 122nd Annual Meeting.

Until next issue, Aufwiederschen!

R. D. Semsch, M.D.
Chairman
Scientific Assembly

Minnesota Society of Clinical Pathologists

Symposium on Endocrine Disorders

Date:	Saturday, April 5, 1975
Place:	Health Sciences Building, University of Minnesota
9:45-10:00 a.m.:	Welcome Address and Announcements—Charles Chedister, M.D., President
10:00-11:00 a.m.:	Histology of the Thyroid Gland in Normal and Abnormal States—Louis B. Woolner, M.D.
11:00-12:00 noon:	Thyroid Function Testing—Colum A. Gorman, M.D.
12:00- 1:30 p.m.:	Luncheon at Campus Club, Coffman Union
1:30- 2:00 p.m.:	Normal and Abnormal Histology of the Parathyroid Gland—Erhard Haus, M.D.
2:00- 2:30 p.m.:	Parathyroid Function Testing—Arnold Lindall, M.D., Ph.D.
2:30- 3:15 p.m.:	Adrenal Gland Function in Normal and Abnormal States—Richard Doe, M.D.
3:15- 3:45 p.m.:	Histology of the Adrenal Gland in Normal and Abnormal States—J. Aiden Carney, M.D.
4:15- 5:00 p.m.:	Endocrine Aspects of Hypertension—David M. Brown, M.D.
7:30 p.m.:	Commemorate E. T. Bell Banquet for friends of Dr. Bell and members of the Society, Sixth Floor, IDS Tower, Catered by the Marquette Inn.
Tuition:	$10.00 (includes luncheon, lecture summaries, and booklet of 35 mm. slides; dinner additional)
Applications:	Before March 15 to: Wayne A. Chadbourn, M.D., Secretary, Minnesota Society of Clinical Pathologists, 900 South 8th Street, Minneapolis, Minnesota 55404
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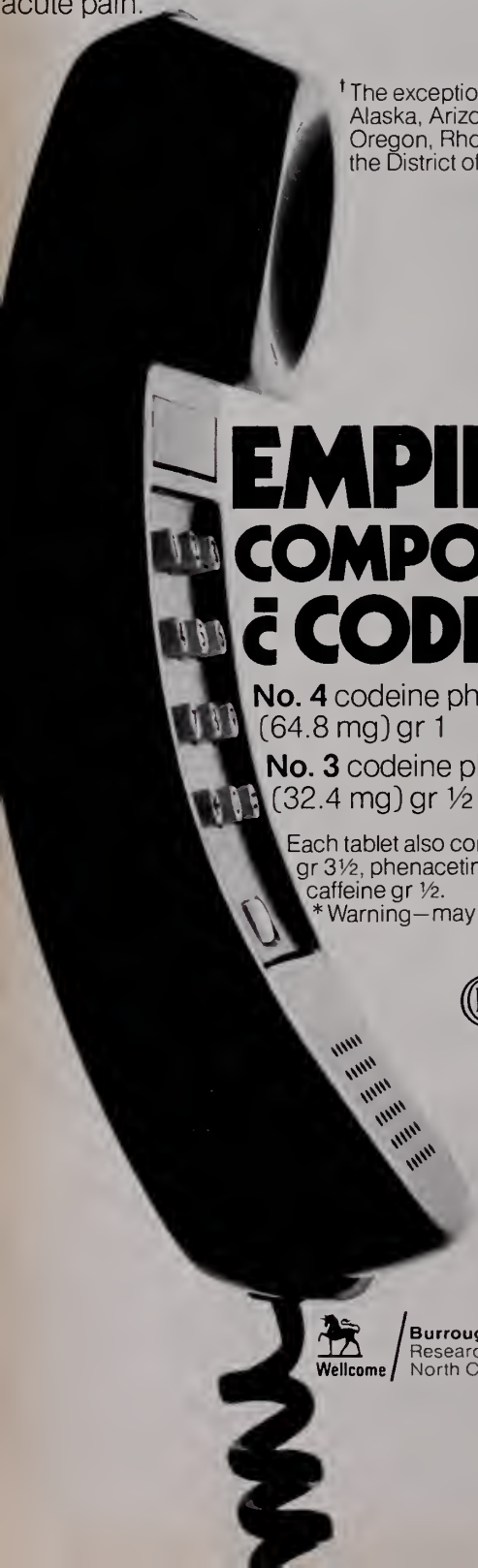
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Child Psychiatry

Adolescence

Phase or Disturbance?

ALEXANDER R. LUCAS, M.D.*

Some of the problems and confusion of the adolescent reflect our uncertainty and changing life styles—and a denigration of values and standards. Adolescents demand to be considered as individuals. Despite their many problems, they have coped successfully with adversities in the past and probably will continue to do so.

Adolescence is the transition from childhood to maturity; it is consequently a phase of life that is characterized by change and transformation. In short, it is the process of growing up. Anything said about adolescence carries with it the hazards of redundancy and overgeneralization: redundancy because all has been said before, and overgeneralization because no matter how characteristically adolescent the problems of our teenagers seem to be, adolescents are all individuals and want desperately to be understood as such. A good example of this was the reaction of a high school senior to a proposed section for a book on adolescence by Irene Josselyn, who perhaps understands the concerns of adolescents as well as anyone over 30. In reply to Doctor Josselyn's question as to whether she had accurately interpreted a certain point of view she had seen as common among adolescents, the high school senior indicated that the interpretation was correct and that she liked the way it was written. However, the girl's remarks did not seem to fully express her reaction and she added,

> "I wish you wouldn't publish that manuscript. You write in generalizations about young people. If my mother reads it she will say, 'Oh, that's why she does that,' and I'm put in a new slot. Young people are tired of being put in slots. We are individuals; we don't really fit in any slot. Each one of us should be understood as the unique individual we all are.[1]"

Normal and Abnormal Behavior

At the risk of making generalizations, I intend to distinguish between those behavior patterns that are appropriate to adolescence and to be expected during adolescence from those that denote disturbance and psychopathologic behavior. Recognizing what is abnormal requires an understanding of normality, and the difficulty is that during adolescence there is tremendous variability of behavior—all of which may be perfectly normal. The adolescent is changeable and unpredictable. The middle-aged person sees the adolescent as being stubborn, rebellious, egocentric, troublesome, obstreperous, untidy, and a know-it-all. His hair is too long, he listens to deafening meaningless sounds he calls hard rock, he is lazy and unmotivated; girls dress like boys and boys like girls until the sexes become indistinguishable. The best way to appreciate the thoughts and feelings of an adolescent would seem to be by recalling one's own adolescence. I find it harder to do each day. The difficulty of the generation gap was brought home to me bluntly by a 13-year-old girl whom I was seeing in a diagnostic interview. Frustrated by my inability to see a situation from her point of view, she shouted, "Weren't you ever my age?"

There has been too much tendency to stress the negative aspects of adolescence. These are most visible. But the adolescent also has an enthusiasm, an altruistic philosophy, inexhaustible energy, and an abiding optimism from which we can learn. The next best way to empathize with the adolescent, if our memory is faulty, would seem to be by reading the descriptions of the adolescent thoughts by some of the novelists: among the best examples are Dostoevsky's penetrating characterization of Alyosha in *The Brothers Karamazov* and Maugham's autobiographical *Of Human Bondage.*

*Head of Section of Child and Adolescent Psychiatry, Mayo Clinic and Mayo Foundation; Associate Professor of Psychiatry, Mayo Medical School, Rochester, Minnesota.

Read at the annual meeting of the Southern Minnesota Medical Association, Winona, Sept. 29, 1973.

Before considering the characteristics of adolescence—the overgeneralizations—I will look at the ingredients that have made a particular teenager what he is today: the unique individual he wants to have others recognize. To view a teenager in isolation without an awareness of the many influences to which he was exposed during his earlier years, and without an understanding of his present family and social environment, prevents us from seeing the true picture. His genetic background and innate temperament, his nurture in infancy, the quality of family relationships he was exposed to during the preschool years, the successes and failures during the elementary school years, and the nature of his peer relationships have all combined to make him what he is. These are developmental concepts with which we are all familiar and which we accept today as almost self-evident. These influences, both favorable and unfavorable, have determined the young adolescent's capacity in many ways: to relate to others in depth or to be shallow and unempathetic; to have a spontaneous, exciting approach to life and its experiences or to be hesitant and fearful; to be comfortable about his sexual identity and gender role or to be uncomfortable in his sexual role and confused by distorted family relationships; and to have achieved a sense of competence and self-worth or to be burdened with lack of security in his abilities and an absence of self-generated motivation.

With some assets and liabilities—one hopes that there are more of the former than of the latter—the child enters puberty. He enters a period of accelerated change. Not since the age of two has the rate of physical growth and development been as great as during the spurt between the ages of 11 and 13 in girls and between 13 and 15 in boys.[2] Internal endocrine and metabolic changes lead to unfamiliar and often troublesome feelings. Accompanying the emotional changes at adolescence are changes in cognitive processes and conceptual thinking elucidated by the studies of Jean Piaget and his co-workers.[3] The child performs concrete mental operations, while the adolescent thinks beyond the present and builds systems and theories. The child does not think about his own thoughts and has no powers of reflection. The adolescent is able to analyze his own thinking and construct theories by what Inhelder and Piaget[3] call second-order thinking. As he is able to criticize his own thinking the adolescent begins to consider himself the equal of adults and to judge them on the same plane as himself; thus he cannot tolerate hypocrisy. He differs from the child in that he thinks beyond the present. He commits himself to possibilities. He dreams of the future and his ideas of changing society.

The adolescent is struggling with an increasing desire to become independent yet he still has many dependency needs. He has a need to be different but also a need to identify with a group. Regardless of the time in history, the adolescent has felt a need to be different from his parents and to develop a unique identity. Yet the strivings for nonconformity often lead to a strong group identification and a high degree of conformity within the group. Characteristically, adolescents become noncommunicative with their parents while needing to communicate actively with their friends. The content of communication is less important than the fact that communication occurs. The usual response of the teenager when asked about the topic of a 20-minute telephone conversation with a friend is, "nothing"—an answer that is most often correct.

Diagnosing Pathologic Behavior

The normal behavior of the adolescent is troublesome enough, and so often is puzzling to us. When does this behavior become pathologic, and how can we identify an adolescent who is emotionally disturbed? Josselyn[1] states that "There is no symptom of the disturbed adolescent that does not in one way or another fit into the category of normal adolescence." I agree with this but I believe that, while adults tend to become too excited about troublesome behavior in an adolescent who is basically well adjusted, they may also ignore inconsequential behavior that may be a sign of deeper disturbance. We should be cautious when advising parents that it is a phase which the youngster will outgrow. It is the *degree* and the *perseverance* of a particular behavior that should alert the physician to investigate a problem in greater depth.

The Table summarizes just some of the sources of adolescent conflict, some examples of normal behavior characteristic of this phase, and their possible pathologic counterparts.

Adolescents commonly have a heightened awareness and preoccupation with the body. This is the result of, among other things, the growth

spurt with its rapid endocrine changes. Excessive hypochondriasis may cause the adolescent to present to the physician a host of physical complaints that cannot be explained by physical disease. Time will be well spent with such a patient to determine his concerns about bodily changes and to clear up various misconceptions. There is too great a tendency to make an organic diagnosis and to overtreat the symptoms, or simply to consider a complaint as being of psychologic origin and to prescribe tranquilizers. Conversion neurosis, a more severe disorder, may occur and will require psychiatric attention. Sexual tension leads to an increase of masturbation during adolescence and to attempts at heterosexual exploration. If adults apply restraint that is too great, inhibitions may develop; on the other hand, if adults set no limits and if they give no guidelines for sexual role behavior, various forms of acting-out will occur. Individual variation may lead to self-doubt in some adolescents who are slower to develop than their age-mates. The resultant loss in self-esteem may lead to various forms of failure, the most common of which we see in academic underachievement. Underachievement and dropping out of school have, of course, many antecedents, and a simple cause-effect relationship should not be inferred.

Rebelliousness is a characteristic of adolescence. We can accept a certain amount of it and can learn to understand the adolescent's need to experiment with greater freedom. In the striving for independence the adolescent's assertiveness can go beyond reasonable bounds and culminate in various forms of delinquent activity. We may see lawful protest progress to bomb-throwing and other dangerous illegal activities. On the other hand, an adolescent who has remained too dependent on the family may show uncertainty in new situations and develop the signs of school phobia.

As a manifestation of the adolescent's desire to be a nonconformist we expect to see changes in his dress and grooming, a rejection of some

TABLE
Aspects of Adolescent Behavior, Pathologic Outcome, and Resolution

Sources of conflict	Normal behavior	Pathologic outcome	Resolution to mature adult personality
Growth spurt			
Endocrine changes	Increased awareness and preoccupation with body	Hypochondriasis Conversion neurosis	Satisfactory heterosexual relationships
	Masturbation, heterosexual exploration	Sexual acting-out	Marriage
Individual variation	Self-doubt	Underachievement Dropout	Self-confidence
Independence vs. dependence	Rebelliousness (lawful protest)	Delinquency Extreme radical political activity	Independent functioning
	Experimentation with freedom	Runaway	Reestablishment of warm relationships with parents on equal level with mutual respect
	Uncertainty of new situations	School phobia	
	Uncommunicative with parents		
Nonconformity vs. conformity	Odd dress and grooming	Self-defeating nonconformity	Selective acceptance of tradition and established values with new values added
	Rejection of adult values	Delinquency	
	Identification with peer culture	Gangs	
	Eating fads	Drug abuse Eating disorder—anorexia obesity	
Optimism vs. pessimism	Lability of mood	Depression, suicide	Sustaining optimism toward life
Philosophic vs. concrete thought	Daydreaming, fantasizing Idealistic theorizing	Psychosis	Productive intellectual endeavors
Goal-orientation vs. hedonism	Fluctuation in motivation	Underachievement Dropout Drug abuse	Productive job identity

parental values, and identification with the peer culture. Carried to the extreme this, too, can lead to delinquency or to a self-defeating nonconformity for its own sake. Serious drug abuse may be the end result of seemingly harmless group experimentation. Significant eating problems—both overeating and self-starvation—occur as exaggerated forms of diet fads in certain adolescents.

Wide-swinging mood fluctuations are normal in adolescence, but actual depressions are frequent as pathologic behavior. They should be recognized when an unhappy mood persists and when there is general withdrawal of interest and inability to concentrate, often in association with various somatic symptoms. The possibility of suicide should be considered because of its significant occurrence during adolescence.

The normal adolescent may become preoccupied with abstract fantasies and idealistic theorizing. Usually this does not portend serious psychopathology, but psychosis can begin in adolescence. Thinking that is overly abstract, illogical, or concrete may indicate serious disturbance, as do incongruous or bizarre behavior and marked changes in personality.

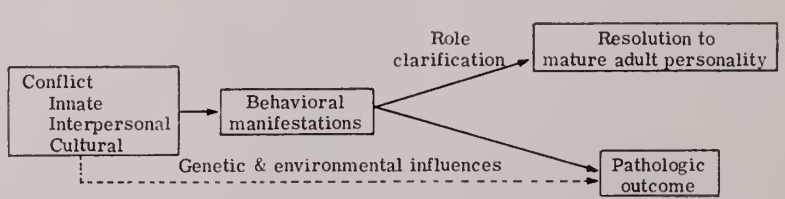
The adolescent is torn between his lofty goals, which he is able to define in his mental constructs, and the pursuit of immediate pleasure and gratification of his impulses. He fluctuates between his desire to change society and his immediate concerns. This is reflected by changes in motivation. The increasingly hedonistic attitude of many people today is surely a reflection of the models they have to identify with. Idealized heroes seem to be a thing of the past. One 16-year-old boy, whom I saw because he had instigated a bomb scare in his school, replied to my question as to whom he admired most by saying, "Evil Knievel." Without consistent models who have a value system and firm convictions of their own, adolescents cannot be expected to develop positive goals or the motivation to achieve those goals.

The severity of psychopathologic disturbance gives an indication as to whether it can be managed by discussion and understanding support, whether psychiatric consultation will be necessary, or, for the most severe problems, whether there should be residential treatment in a hospital-based program that provides psychiatric treatment, milieu therapy, and residential schooling.

Needs of Adolescents

Rabinovitch[4] has described five areas about which adolescents need clarity: (1) role in the family, (2) sexual role, (3) role in school, (4) job future, and (5) value system. Much of adolescent behavior, normal and pathologic, can be understood in terms of these needs. The need for role clarification has to be met by the adults in the adolescent's life. Clarification of these roles diminishes the conflicts and allows adolescent behavior to be resolved comfortably. The results of such conflicts are shown schematically in the Figure. How these needs should be met cannot be discussed in detail here but we, as adults, do have to clarify some of these roles for our adolescents by example and by being certain ourselves what we want to convey.

With respect to value systems, Rabinovitch[4] states categorically that "Adolescents cannot establish their own value scales," and I agree wholeheartedly. Adolescents will reflect the values or lack of values of their elders. Today's American adolescent has no clearly demarcated standards and guideposts. He is constantly buffeted by unclearly formulated internal ideas, alternating parental pressures and permissiveness, conflicting influences from other adults, confusing exposure to the news media, and influences from his peers. From these diverse influences he is expected to make his decisions. Worst of all, many of the individuals, including parents, to whom the adolescent is exposed have no firm convictions of their own; in Josselyn's words, "The adolescent of



Figure—Outcome of conflicts in adolescence.

today is exposed to an unusually large number of people who have no consistently formulated value system.[1]"

Through clarification of roles, the adolescent can develop a mature adult personality. He will gain in self-confidence and attain a comfortable sex role identity leading to satisfactory heterosexual relationships, culminating in marriage and family. His experimentation with freedom within a framework of judicious limits will lead him to a level of independent functioning. Following a period of uncommunicativeness he will reestablish warm relationships with his parents on an equal level with mutual respect. In the mature personality there will be a selective acceptance of tradition and established values with new values added. Mood swings will give way to a sustaining optimism toward life. His daydreams and fantasies made possible by second-order thinking come to fruition in productive intellectual endeavors. Self-generating motivation sustains the adolescent in his search for a productive job identity and his ultimate discovery of his place in his world.

Conclusion

I have suggested that some of the problems and some of the confusion of the adolescent reflect our own uncertainty and changing life styles—and a denigration of values and standards. When many of the events taking place in our communities and in our country as a whole are considered, there is dire cause for alarm. But I have confidence in the adolescents themselves. They have coped successfully with adversities in the past and have even improved the lot of succeeding generations. I think they will continue to do so.

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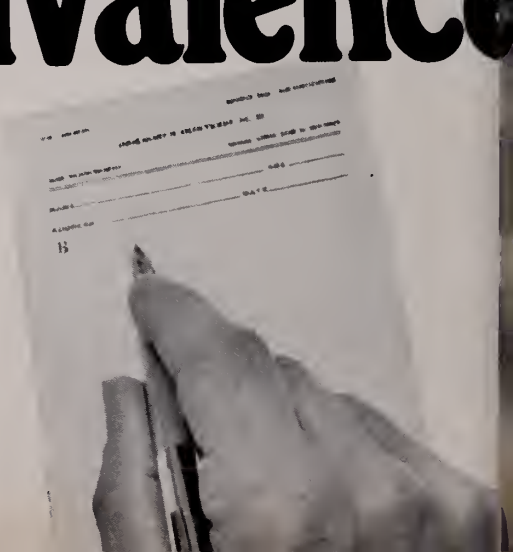
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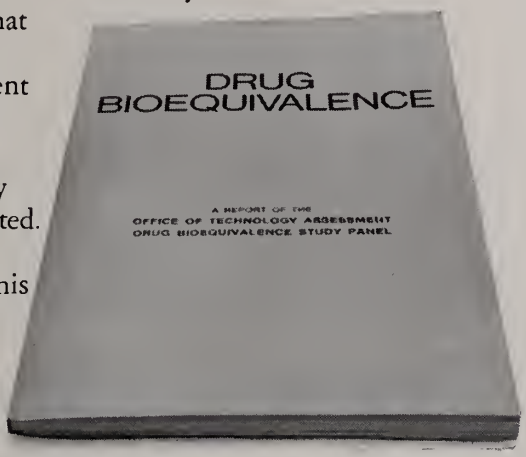
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(Continued on Page 292)

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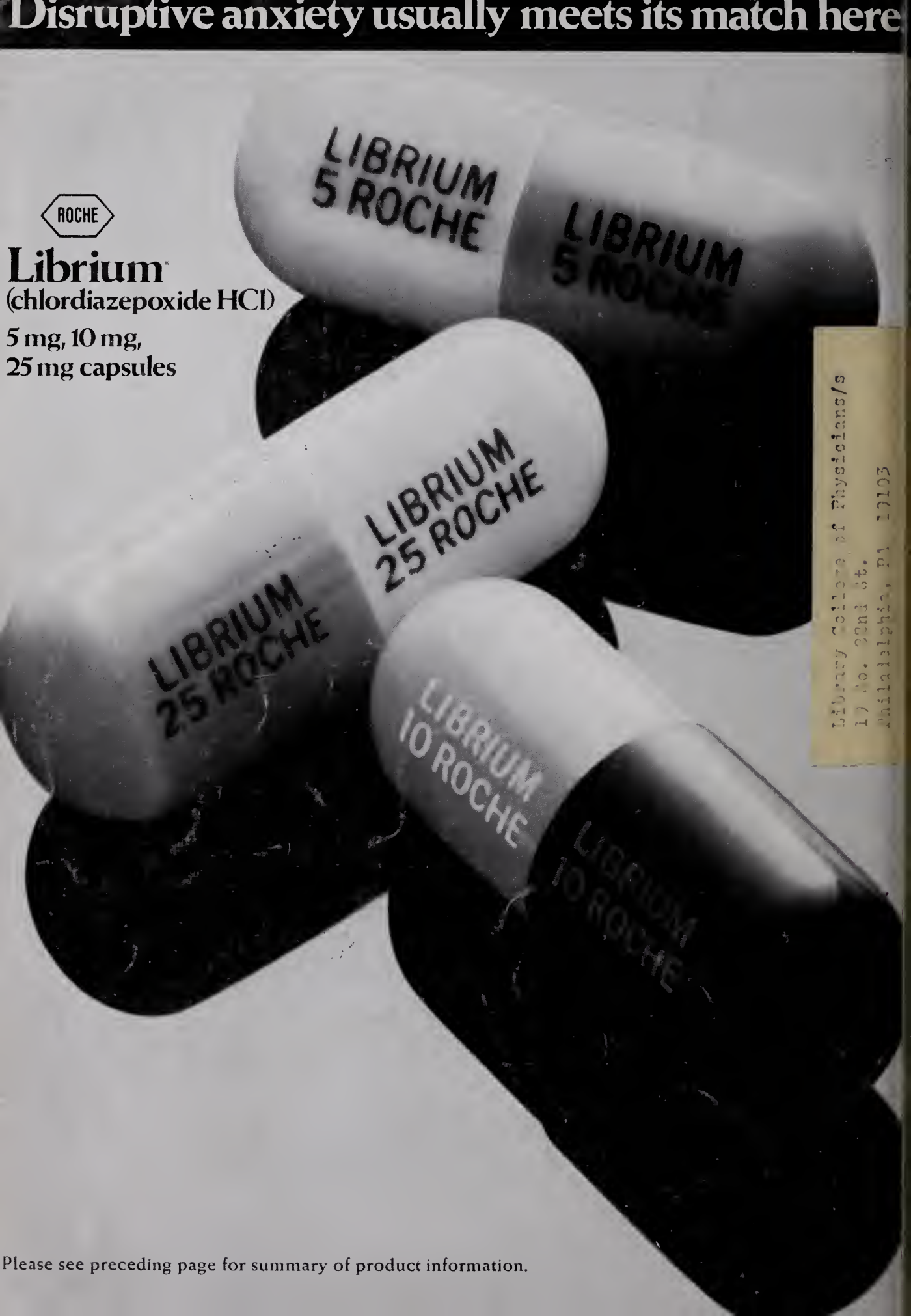
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respond to one

According to her major
ıptoms, she is a psychoneu-
c patient with severe
iety. But according to the
cription she gives of her
ings, part of the problem
y sound like depression.
s is because her problem,
ıough primarily one of ex-
sive anxiety, is often accom-
ied by depressive symptom-
logy. Valium (diazepam)
provide relief for both—as
excessive anxiety is re-
ed, the depressive symp-
ıs associated with it are also
n relieved.

There are other advan-
es in using Valium for the
ıagement of psychoneu-
c anxiety with secondary
ressive symptoms: the
chotherapeutic effect of
ium is pronounced and
id. This means that im-
vement is usually apparent
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anxiety states
with associated
depressive symptoms

veillance because of their predisposi-
n to habituation and dependence. In
gnancy, lactation or women of child-
ring age, weigh potential benefit
inst possible hazard.

cautions: If combined with other psy-
tropics or anticonvulsants, consider
efully pharmacology of agents em-
yed; drugs such as phenothiazines,
cotics, barbiturates, MAO inhibitors
other antidepressants may potentiate
action. Usual precautions indicated in
ents severely depressed, or with latent
ression, or with suicidal tendencies.

Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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President's Letter

Cooperation and Collaboration

IT IS WITH MUCH appreciation that I accept the generous offer by Dr. Barnard Hall to utilize the lead-off page in MINNESOTA MEDICINE, that is normally assigned to his President's Message for a message of my own.

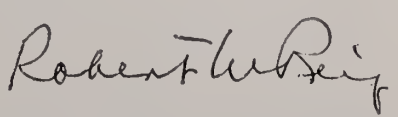
If I could summarize the essence of what I want to say to our conjoined membership, it would be with the words, "cooperation and collaboration". Never has there been a time when such a relationship between us was as important to our welfare as it is now. Our professional integrity, the freedom to care for the needs of our patients according to the dictates of good medical judgment, and the very basic relationship we and our patients experience, all are under attack by governmental bodies.

It is very simple to cite an example of this threat, by referring to the recent Federal regulations that required (before their implementation was "postponed") preadmission screening before our patients could be admitted to the hospital. Or better, let us look at some of the health bills before the present State legislature. With generic substitution and forced employment of some physician-specialists by hospitals as two specific evidences of the active intervention by legislation into the area of physician-patient relationship, we must see that there are efforts to place physicians under more control. We can respond much more effectively to these attempts if we do so in a coordinated fashion. I would like to suggest that we should consider several courses of action by our members.

We could begin a closer association with more exchange of information at the level of our governing boards. The decisions reached at these levels, were they known by both organizations, frequently could aid in making additional or related decisions that would have a greater impact on health care of the citizens of the state by the very fact that there is a continuity and progression of efforts by both of our associations. This sharing of information could be carried out, at least by some of our committees. Certainly, it would make sense to encourage both of our public policy committees to coordinate their work in the area of legislative contact and testimony.

This is not meant to suggest at all, that either of our organizations should lose the independence of action that it enjoys now. There will continue to be times when the interests of the Academy of Family Physicians will dictate the need for us to pursue a course that is separate from that of other professional medical groups. Likely, these times will be relatively few in number. Much more frequently, our interests are truly congruent with those of the Minnesota State Medical Association and we should be working together at all levels. The same could be said for many other medical specialty organizations in the state.

A typical example of this cooperation and collaboration is given by the way our associations are working together on the certification of members in the area of continuing education. The evidence now is that in order for the MSMA to carry out this work in education, this coordinated effort is a necessity. If we are to be effective in many other areas, it is likely that the same sort of union of effort will be required. Let us begin to implement this as soon as possible.

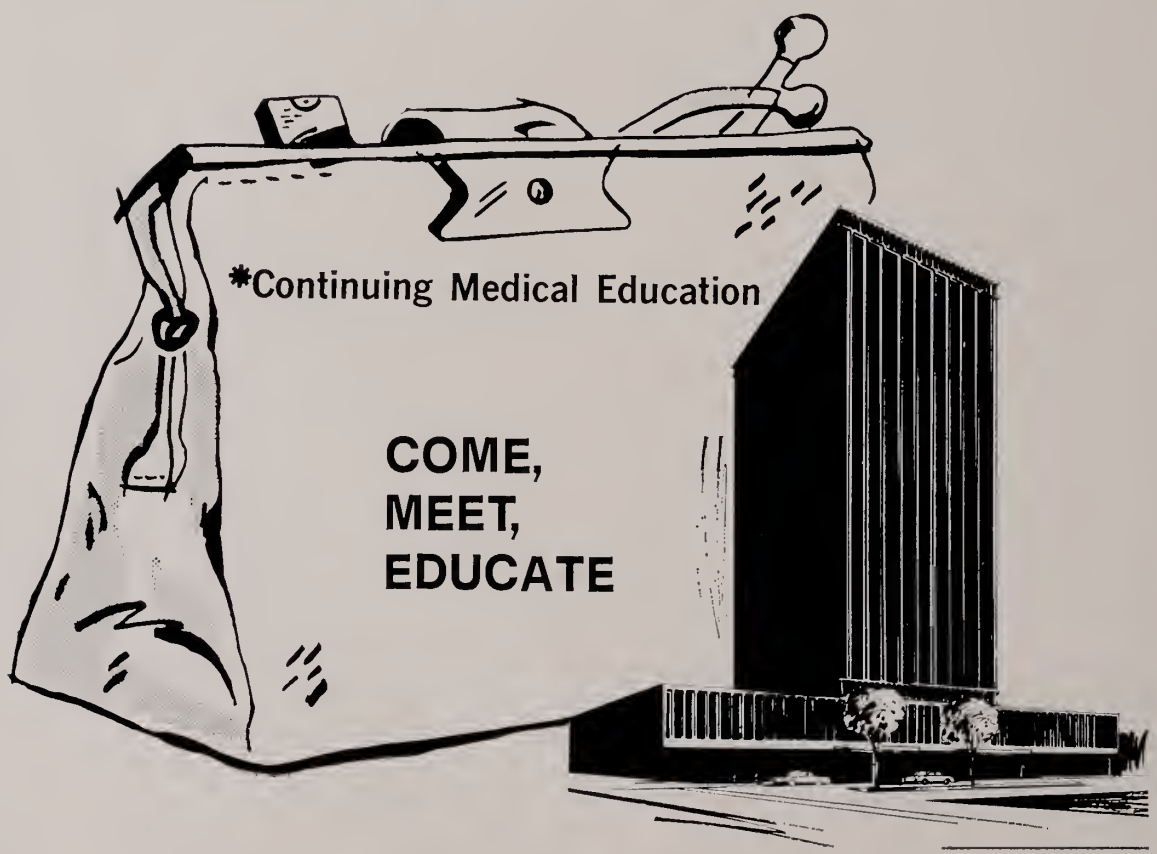


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MINNESOTA STATE MEDICAL ASSOCIATION

122nd Annual Meeting

CME*



MAY 22, 23, 1975 ST. PAUL HILTON HOTEL

Editor's Notebook

Parameters of Parameter

This weekend I was leafing through *Strictly Speaking,** a new book by Edwin Newman. Newman is a television commentator who knows, writes, and speaks the King's English. In his book he takes a genial poke at stale, imprecise, pretentious words. In this category he places *hopefully, ongoing, dialogue, thrust, viable,* and *parameter.*

Of *parameter* he says: ". . . if there is one word that expresses the spirit of the age, it is *parameter,* a mathematical term now widely misused so that nobody finds himself in the hateful position of having to say boundary or limit."

His comment brings to mind an old essay of mine, "Parameters of Parameters."† Perhaps by reprinting a portion of it now, I can help Ed Newman in his campaign to deflate the language.

> "Physicians frequently write about *parameters.* Yet as far as I know, they have never defined precisely what *parameters* are. Why do they use the word? Because, I suspect, *parameter* implies measurement. In these days of biological flux, anything that can be measured should be understood.
>
> "If writers are uncertain about *'parameters,'* readers are more so. I asked ten doctors to define the word. Answers varied from "any measurement"; "variables influencing a clinical measurement"; "function tests of an organ system"; "a term describing intrinsic rhythms in biological systems" to "I don't know, do you?"
>
> "In despair, I turned to *Stedman's Medical Dictionary* and *Dorland's Medical Dictionary.* Neither defined *parameter* as it is currently used. I will not repeat what *Stedman's* said, but *Dorland's* tried to fog this by me:
>
> *'Parameter*—an arbitrary constant, the value of which characterizes the mathematical expressions into which it enters, e.g. rheobasis and chronaxie as parameters of the excitability of nerves (Lapicque).'
>
> "Then I investigated conventional dictionaries.
>
> *Oxford Universal Dictionary* put me into the hinterlands of obscurity with this offering:
>
> '. . . *Gen.* A quantity which is constant (as distinct from ordinary variables) in a particular case considered, but which varies in different cases; esp. a constant occurring in the equation of a curve or surface, by the variation of which the equation is made to represent a family of such curves and surfaces.'
>
> "A *parameter,* then, would appear to be a variable constant. A radius, for example, would be a *parameter* of a circle. Vary

*Strictly Speaking, Edwin Newman, The Bobbs-Merrill Company Inc., Indianapolis/New York, 1974, $7.95.
†Reece RL: Parameters of Parameter, Hartford Hospital, Bulletin, 18:224, 1963.

the circle, and you vary the *parameter*. What could be more useful for the artful scientist then a variable constant especially if he goes around in academic circles?

"When I could not apply these definitions to medicine, I decided to dig to the roots of the matter. After all, -meter came from the Latin word, *metron* to measure. All that remained was *para*. Once its meaning was clear, the puzzle would fall together. *Para* can mean beside, along side, beyond or amiss. Of what, therefore, is a *parameter* a measure? It would appear to measure everything but the object of measurement.

"Next I thought of studying *para* as a prefix to other medical words. Some precedents are: paranoia (faulty or deranged), parasympathetic (associated in a subsidiary or accessory capacity), and paratyphoid (closely resembling the true form). Is a *parameter* a faulty or deranged measurement, an accessory or subsidiary measurement, or does it just resemble a measurement? I confess I do not know.

"I consulted the *Index Medicus*. There I found three references.[1-3] The first was a verse. Doctor Stanley Schor, Director of the American Medical Association's Department of Biostatistics, composed the second.[2] He states:

'If a characteristic is measured or counted in a sample, the value or concept is called a statistic; if the same characteristic is measured or counted in the population from which the sample comes, the value or concept is called a *parameter*.'

"That sounded logical and clear, and it came from an authority. But shortly after, a disgruntled reader wrote to the *Journal of the American Medical Association*. He not only disagreed with Doctor Schor but quoted John Kelley, a well-known American mathematician.[3] In a footnote in his textbook, Doctor Kelley commented:

'I'm not sure what a *parameter* is, but I think you call a number a *parameter* when you're thinking about a function whose domain is a set of numbers.'

"Now, with nowhere to turn, I put the question to myself—What is a *parameter?* I believe (but I'm not sure) a *parameter* is a measure of a phase or function of a biological process. It does not reveal the entire process but gives perspective. Taken singly, a *parameter* distorts the whole. Perhaps the following verse will show what I mean.

'It was six men of Indostan
To learning much inclined,
Who went to see the elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

The First approached the elephant,
And, happening to fall
Against his broad and sturdy side,

At once began to bawl:
"God bless me! but the elephant
Is nothing but a wall!"

The Second, feeling of the tusk,
Cried: "Ho! what have we here
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an elephant
Is very like a spear!"

The Third approached the animal,
And, happening to take
The squirming trunk within his hands,
Thus boldly up and spake:
"I see," quoth he, "the elephant
Is very like a snake!"

The Fourth reached out his eager hand,
And felt about the knee:
"What most this wondrous beast is like
Is mighty plain," quoth he;
"'Tis clear enough the elephant
Is very like a tree."

The Fifth, who chanced to touch the ear,
Said: "E'en the blindest man
Can tell what this resembles most;
Deny the fact who can,
This marvel of an elephant
Is very like a fan!"

The Sixth no sooner had begun
About the beast to grope,
Than, seizing on the swinging tail
That fell within his scope,
"I see," quoth he, "the elephant
Is very like a rope!"

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!

So, oft in theologic wars
The disputants, I ween,
Rail on in utter ignorance
Of what each other mean,

And prate about an elephant
Not one of them has seen!
John Godfrey Saxe'

"Some investigators, after blindly feeling similar brutes in biological jungles, dignify their gropings by introducing the *parameter.*

"This essay would be incomplete if I did not suggest substitutes for *parameter.* I have come up with these:

equivometer, ambiguimeter, circullocumeter—All of these, I trust, explain themselves.

fragmontage—This Gallic-spiced term suggests a measure of a montage, and a montage, of course, is a composite picture made of intertwining superimposed, heterogeneous elements.

nyctameter—In Greek, *nycta* means darkness or night.

ombrameter—Similar to nyctameter, but *ombra* means shadows.

periobiometer—This mellifluous word suggests measurement at the periphery of life.

I doubt if any of these terms will replace *parameter,* but any would serve as well."

Richard L Reece MD

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Mycosis Fungoides

Clinical Features of 22 Patients

MARK V. DAHL, M.D.*

Twenty-two patients with the lymphoreticular neoplasm mycosis fungoides were admitted to University of Minnesota Hospitals between 1960 and 1974. In many patients, the initial diagnosis was psoriasis. Eight patients are known to have died. All eight had previously developed cutaneous ulcers or tumors. No patients developed erythroderma. Multiple therapeutic approachs were employed, but no single one was universally better or prevented death. This study supports the need for a multicentered prospective study of classification and therapy of mycosis fungoides.

MYCOSIS FUNGOIDES is a malignant lymphoreticular neoplasm appearing in skin. The disease was originally named mycosis fungoides because cutaneous tumors resembled mushrooms.

Often the disease remains confined to the skin for many years. Death may occur with or without evidence of internal organ involvement.

The purpose of this report is to review the University of Minnesota experience with mycosis fungoides over 14 years.

Methods

Patient clinical records were reviewed retrospectively. All inpatient records coded for mycosis fungoides between January, 1960 and July, 1974 were reviewed. Records coded for Hodgkin's disease, reticulum cell sarcoma, or other diagnoses were not reviewed.

Results

Twenty-two patients were admitted to University of Minnesota Hospitals with a coded diagnosis of mycosis fungoides between January, 1960 and July, 1974. Males outnumbered females 14 to eight. The mean patient age at onset was 51. Mycosis fungoides often began at a younger age in females than in males. The onset of mycosis fungoides occurred before age 50 in four of eight females (50%) but in only four of 14 males (29%). Mean age at onset was 43 for females (range 9-69), and 52 for males (range 30-80). All patients were Caucasian.

Skin Biopsies

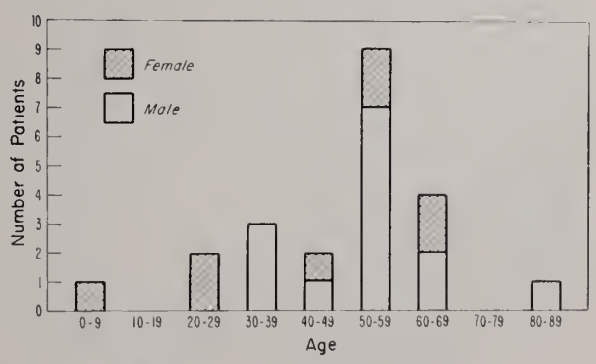
Skin biopsies were performed on all patients. At least one biopsy from each patient was diagnostic or compatible with mycosis fungoides. Often multiple biopsies from a given patient were nonspecific, while one other biopsy taken during the same admission was diagnostic.

Bone Marrows

Bone marrow aspiration, bone marrow biopsy, or both were obtained in 19 patients. Most were normal, and the remainder were non-diagnostic. PAS stains of bone marrow cells occasionally revealed PAS-positive granules but definite Sézary cells were not seen.

TABLE

AGE AT ONSET



Age of onset of mycosis fungoides.

*Department of Dermatology, University of Minnesota Hospitals, Minneapolis, Minnesota.

Address reprint requests: Box 98 Mayo, University of Minnesota Hospitals, Minneapolis, MN 55455.

Lymph Node Involvement

Generalized lymphadenopathy was present in only eight patients. Biopsy showed lymphoreticular malignancy in four. Lymphangiograms were performed on 11 patients and were negative in all but one. This patient had generalized lymphadenopathy including easily palpated nodes. Lymph node biopsy showed lymphoreticular malignancy.

Other Features

Liver-spleen scans were performed on five patients. None were abnormal. Liver function tests including serum glutamic-oxalacetic transaminase, alkaline phosphatase, and serum bilirubin were normal when first determined in all patients tested.

Erythematous plaques were the most common cutaneous lesions. Scaling was frequent. The initial diagnosis was often psoriasis. Other initial diagnoses included tinea corporis, intertrigo, pityriasis rosea, and alopecia. No patients presented with or developed erythroderma.

Mortality

Eight patients are known to have died. The overall mortality rate was 36%. All deaths were directly related to mycosis fungoides or specific therapy.

Ulcers or tumors had developed in 12 patients (55%). Eight of these patients have died (67%). Of the remaining four patients, two have been lost to follow-up and the other two have developed ulcerations or tumors for the first time only within the past year. The range of patient survival after development of ulcers or tumors ranged from one to 15 years. No patient has died without developing ulcers or tumors prior to death.

Of the eight patients who developed lymphadenopathy, four patients have died (50%). Lymph node biopsy of enlarged nodes among patients who died showed lymphoreticular malignancy in three patients and hyperplasia in one patient. Lymph node biopsies of the four remaining patients showed either lipomelanotic reticulosis (dermatopathic lymphadenopathy) or hyperplasia, but no histologic evidence of malignancy in the node.

Treatment

Patients were treated by various approaches and chemotherapeutic drugs. No patient received electron beam therapy. Twelve patients received radiation therapy. Eleven patients were treated with topical applications of nitrogen mustard. Two developed allergic contact dermatitis to nitrogen mustard. In general, most patients responded well to this therapy. One patient was treated with topical bischloroethylnitrosourea (BCNU) and one patient was treated with topical uracil mustard. Ultraviolet light, topical corticosteroids, and a myriad of systemic chemotherapeutic agents were also employed. No treatment was clearly superior to others in preventing death or dissemination of disease.

Comment

Mycosis fungoides is an uncommon disorder. Despite the fact that the University of Minnesota Hospitals serves as a referral center, only 22 patients with mycosis fungoides have been admitted here in the 14 year period between 1960 and 1974.

In this series as in most others,[1] males are afflicted more commonly than females, although the sex difference is usually less marked than the 14 to eight male predominance reported here. Males are particularly more likely than females to be afflicted with a generalized erythroderma or the d'emblee type of mycosis fungoides in which tumors arise without a preceding plaque or erythrodermic phase.[1]

As in most other series, the average age at onset was lower in females than in males.[1] The youngest patient was nine years old which is unsual, but onset as young as age eight months has been recorded.[2] Most patients develop mycosis fungoides between ages 40 and 60.[1] The disease is perhaps less common in Negroes than in Caucasians.

The clinical manifestations of mycosis fungoides are capricious. Pruritus is common, and may be generalized, severe, intractable, and out of all proportion to objective physical changes of the skin. It does not respond well to antipruritic measures including hydration and systemic antihistamines.

A single skin biopsy by no means rules out a diagnosis of mycosis fungoides. Among most patients, skin biopsies from some areas were banal and nonspecific, while others were diagnostic for mycosis fungoides. In general, multiple biopsies should be obtained from the most infiltrated lesions in multiple areas.

Skin Lesions in "Premycotic" Phase

Skin lesions in the early "premycotic" phase include erythematous patches or plaques, urticaria, scaling patches or plaques, or even bullae (Figure 1). Cutaneous lesions are very often misdiagnosed at this stage as psoriasis, intertrigo, eczema, pityriasis rosea, or other common papulosquamous dermatoses. Poikiloderma, alopecia mucinosa, and parapsoriasis more readily suggest mycosis fungoides (Figure 2). Early lesions may be evanescent and clear spontaneously with or without therapy, while others may remain for long periods virtually unchanged.



Fig. 1—Typical patch of mycosis fungoides occurring on upper chest. This type of lesion may be mistaken for various benign dermatoses.



Fig. 3—Patches may become infiltrated and ulcerations may develop.

Gradually patches may become infiltrated (Figure 3). In some patients, mycosis fungoides presents with infiltrated plaques. These are often brick-red and shiny. A diagnostic sign when present is a blue halo outlining brick-red plaques.[1,3] Another clinical feature is the tendency of lesions to involute centrally to produce arcuate, annular, or gyrate patterns (Figure 4). An erythematous, infiltrated, crescent-shaped lesion suggests mycosis fungoides. Plaques often vary in the amount of thickening and infiltration as do different areas of the same plaque.[1]



Fig. 2—A poikilodermatous patch more strongly suggests mycosis fungoides.



Fig. 4—Serpinginous and arcuate lesions result from a tendency of mycosis fungoides plaques to resolve centrally.

As the disease progresses, nodules and tumors often arise in preexisting infiltrated plaques (Figure 5) but may arise from normal skin. Ulceration is frequent over tumors. Ulcerations over plaques are also common. The patient usually attributes initial ulceration to trauma.

Appearance of Tumors or Ulcers

The appearance of tumors or ulcers is an unfavorable prognostic sign. Of twelve patients who developed tumors or ulcerations, at least eight have died. Epstein, in a series of 144 patients including one of ours, found that 50% of patients died of mycosis fungoides within two and a half years after the development of tumors.[4] Ulceration of the skin indicated an even worse prognosis. Only three of our 12 patients (25%) with ulcerative skin lesions of mycosis fungoides died within two and a half years, although two were lost to follow-up and two have had ulcers less than two and a half years.

Lymphadenopathy

Lymphadenopathy is another unfavorable prognostic sign, particularly if biopsy shows lymphoreticular malignancy. Three of four patients with malignant cells in lymph node biopsies have died. The other has lived for only two years since lymphadenopathy developed.

Prognosis

Although general statements can be made, predicting prognosis is difficult. A patient is reported who lived 35 years with mycosis fungoides.[5] One of our patients lived 15 years after first appearance of cutaneous ulcers. Most patients with mycosis fungoides die within five to 10 years.[6,7] About 20% of patients may live more than 10 years.[8]

Treatment

Treatment at present must be individualized. Topical application of nitrogen mustard often produced gratifying results, but allergic contact hypersensitivity to the mustard may develop.[9] Radiation therapy is often palliative. Treatment with low voltage electron beam, if available, offers another alternative.[10] Grenz rays, ultraviolet light, topical corticosteroids, topical uracil mustard, and topical nitrosoureas are other useful modalities for certain patients. In general, when internal organs are involved, systemic chemotherapy or deep radiation therapy are necessary.



Fig. 5—Mushroom-like tumors may arise from preexisting plaques. In the d'emblee form of mycosis fungoides, tumors arise from clinically normal skin.

Capricious Course

Because the disorder is rare, any individual investigator encounters relatively few patients, making controlled, prospective clinical studies of disease staging and effect of various therapeutic modalities difficult. The capricious course of mycosis fungoides further frustrates single-investigator clinical studies. A multicentered approach seems warranted and a Mycosis Fungoides Cooperative Study Group has been established at medical centers throughout the United States funded by the National Cancer Institute. A prospective protocol for evaluation and treatment of patients with mycosis fungoides is currently being written. This study supports the need for such a multicentered prospective approach to treatment of mycosis fungoides.

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Skin Application of Electrical Impulses for Relief of Pain

In Chronic Orthopaedic Conditions

WALTER INDECK, M.D.* AND ANDREA PRINTY, R.N.

This technique is a non-invasive, well tolerated and effective method to treat patients with chronic pain conditions.

In the past few years several authors have reported their successes in using electrical impulses to block the pathways of transmission of pain. Some investigators have inserted miniature electrodes adjacent to the cord in an effort to block the ascending pathway;[5,6] others have used the superficial application of electrical impulses to various areas of the skin for the same purpose.[3]

We have used this modality to relieve pain in chronic orthopedic pain problems, which may present frequently as a complication of degenerative joint disease, injury and complex reconstructive procedures. In neck and low back orthopaedic problems, any of these three factors may exist alone, but frequently two or three may combine and potentiate the ultimate pain severity. These patients become the "unwanted" problems in practice. Hopefully, in these chronic situations, if the pain pathways that exist can be broken even for a short time, patients might then be able to gradually overcome their disability.

Pain is a private sensation whose magnitude is known precisely only by the patient. By serving as a warning signal to an individual it has a beneficial effect. Should it continue for any prolonged period, a patient's reaction may become a completely different pattern of responses; no longer only with a "flight from fear purpose," but possibly offering the patient an added secondary gain.

Pain is a universal experience and probably the motivating factor for most patient visits to their physician. It may be the first symptom of many conditions and accompanies other disabling diseases in their later stages.

Pain is poorly understood. There are three commonly proposed theories.[4,7]

The "specificity theory" is traditional and holds that the sensation of pain is the result of specific peripheral nerve excitation. The impulse is then transmitted in a similar manner as touch, cold and warmth. Free nerve endings have been considered as the most probably pain "end organ" and once stimulated transmit the impulse through specific tracts to a central pain center—whether it be the thalamus or the cerebral cortex. Objections to this theory are based on the findings that different sensations from an area such as the cornea can be appreciated—yet, end organs usually identified with cold and heat are *not* visible microscopically; only free nerve endings are found. The specificity theory does not explain how emotions can inhibit or exaggerate the degree of pain perception.

The "pattern theory"[7] suggests that stimulus intensity evokes a specific "pattern" and this is subsequently interpreted by the brain. This could explain how extremes of heat and cold evoke painful responses.

The end result then, is not the stimulation of a specific end organ, but the result of intensity and frequency of stimulation of a non-specific end organ. Those opposing this theory challenge it because it is too general and does not explain the reason that we can identify some specific end organs.

The "gate control theory"[4] has as its basic concept a T cell that acts as a transmission cell to the dorsal horn. There may be several interacting systems: (Figure 1)

*Attending Staff, Department of Orthopaedic Surgery, Hennepin County General Hospital, Minneapolis, Minnesota and Orthopaedic Surgeon, St. Louis Park Medical Center, Minneapolis, Minnesota and Clinical Associate Professor, University of Minnesota, Minneapolis, Minnesota.

1. Substantia gelatinosa "T" cells.
2. Input fibers from the afferent nerve.
3. Ascending or descending impulses from the dorsal column to the substantia gelatinosa.

The afferent impulses that come through either small or large fibers are affected by the substantia gelatinosa, exaggerating or inhibiting the transmission of the pain impulse. Diagramatically, (Figure 1) if we accept the core of the substantia gelatinosa as the T cell, the input may be from either a small or large nerve fiber. Input from a large fiber creates a significant excitation within the substantia gelatinosa, resulting in a fractory period to inhibit the transmission of pain impulses from the smaller pain-transmitting fibers. Small fibers when stimulated lack this inhibition. This theory can also explain the emotional modification of pain because cerebral or dorsal column descending fibers may act in the same positive way as the large nerve fibers to create excitation within the substantia gelatinosa and subsequently inhibit the transmission to the T cell.

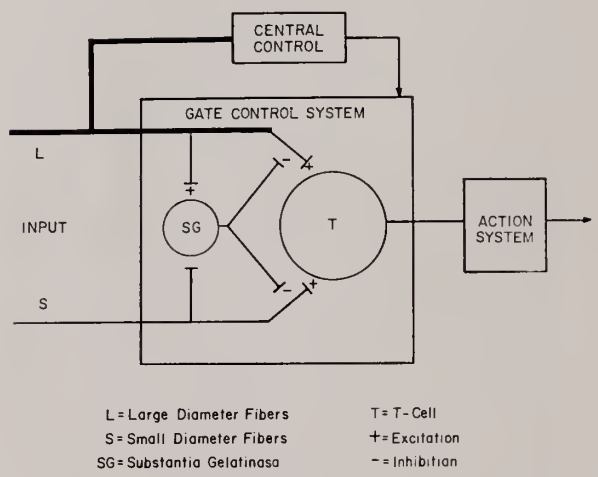


Figure 1

Pain, unlike touch and temperature, probably represents an exaggerated response to a stimulus, possibly even within the touch and temperature receptor organs. The stimulus may be exaggerated and thus produce pain so that perception becomes a function of the type and strength of the impulse irrespective of the skin of stimulus.

Neurophysiologically, we associate the stimulus with an increased permeability of the nerve sheath at the point of excitation. As this change in permeability increases, a potential difference is created in respect to the adjacent area and an electrical action potential is generated. The pain pathway then becomes a sequence from the receptor organ following the nerve root to the sensory ganglion. Recently, neurophysiologists have identified between the sensory ganglion and the dorsal column—the substantia gelatinosa. From the dorsal column the path continues to the thalamus and most probably through the limbic system to the post-central gyrus for interpretation and reaction by the brain.

The gate control theory serves to explain how use of electrical stimulation may be effective in preventing pain impulses from reaching the cortex. The electrical stimulation can create impulse transmission within the large fiber and stimulate enough positive excitation to subsequently inhibit pain impulses. Should the implant be placed in the dorsal column adjacent to the cord, it can act in a similar fashion by exaggerating the number of descending modified impulses.

The T cell firing depends then on the results of gate transmission which, in turn, becomes the resultant of fiber excitation within the substantia gelatinosa and the potentiating or modifying centrol control influence.

Technique

Treatment with electrical impulses depends on



Figure 2

the ability to stimulate the large fibers with a low strength current. There are many types of stimulators and several types of impulse patterns. At the present time, we are using a stimulator that offers a "square pulse" pattern and is relatively comfortable when applied to the skin. (Figure 2). A true action potential wave may be more peaked in amplitude, accomplishes the same effect, but appears to be more unpleasant as it is applied to the skin. Transcutaneous or skin surface application is accomplished by application of the conducting pads to various trigger zone areas, acupuncture sites or even peripheral nerves. Investigators have reported satisfactory relief of low back syndromes by stimulation of the ulnar nerve in its canal behind the medial epicondyle.

An electrical impulse is generated by a battery powered source and can be modified in the pulse amplitude, rate and duration. One of the units that we presently use is slightly larger than a package of cigarettes, quite comfortable and yet produces a sufficient power source to inhibit pain (Figure 3).

Skin irritation at the site of electrode application has been diminished by the recent use of a carbonized rubber electrode applied with a tincture of Benzoin interface (Figure 4).



Figure 3



Figure 4

A trained nurse applied the electrode to an area adjacent to the trigger zone of tenderness, if relief was not obtained, sites both proximal and distal to the area were tried empirically.

The patient was then taught to control the amplitude, frequency and duration of the stimulation for his own comfort and continued self-application, while at home or on the ward.

The treatment in the chosen areas could sometimes take a constant application of the conductors for a twenty-four hour period. This seemed to be best tolerated on an in-patient basis. On the out patient basis, it was necessary for the patient to cooperate in the proper application of the conducting pads in order to obtain relief. At times, skin irritation was present at application sites, but disappeared when the electrical impulse was discontinued.

Patient Study

Fifty patients with low back problems were studied in an out-patient setting and forty were admitted to a "pain ward."

Patients had experienced their pain patterns for varying periods between one and twenty-three years. In the instance where pain was present for twenty-three years, and in another for nineteen years, neither obtained relief from electrical stimulation; otherwise, there did not appear to be a significant correlation between the duration of symptoms and the success of the program.

Forty-five patients complained of radiating extremity pain suggesting some degree of residual root irritation. Most symptoms were "stress ag-

gravated, rest relieved" and even in patients where flexion and extension x-ray studies suggested appropriate level fusion.

Diagnostic studies in most patients had been completed relatively recently prior to evaluation and repeat myelograms or discograms were not performed.

In-patient statistics revealed that twenty of forty patients claimed significant improvement to place them in either good or excellent categories, but only twenty of fifty out-patients showed significant improvement (Table 1).

TABLE 1
Low Back Syndrome

	Inpatient	Outpatient
Unimproved	20	30
Fair	0	5
Good	12	8
Excellent	8	7
Total	40	50

Twenty of forty in-patients with cervical syndrome showed some response to electrical stimulation; seven of eleven out-patients showed some improvement. Only twenty-two of the total patients had undergone surgery usually an anterior exploration and dowel graft fusion of the involved cervical vertebrae (Table 2).

TABLE 2
Cervical Syndrome

	Inpatient	Outpatient
Unimproved	10	4
Fair	2	1
Good	4	5
Excellent	4	1
Total	20	11

A sub-division was made within this group of patients to separate those with neck and headache disability from others experiencing neck and upper extremity pain. A comparison of these subdivisions did not show any significant change in response to electrical stimulation (Table 3).

TABLE 3
Neck and Headache—32 Patients

	Inpatient	Outpatient
Unimproved	4	10
Fair	0	4
Good	5	5
Excellent	1	3
Total	10	22

The other tables have been inserted for informational purposes and no attempt has been made to analyze these results because the categories represent only a few patients (Tables 4-6).

TABLE 4
Arthritis—Rheumatoid and Osteoarthritis
Out-Patient Therapy

	Knees	Wrist
Unimproved	1	1
Fair	1	1
Good	2	1
Excellent	1	0
Total	5	3

TABLE 5
Phantom Pain—Six Patients
Outpatient Therapy

Unimproved	2
Fair	1
Good	1
Excellent	2

TABLE 6
Post Herpetic Neuralgia—Four Patients
Out-Patient Therapy

Unimproved	2
Fair	1
Good	1
Excellent	0

Category determination was primarily subjective. Classification depends upon the patient's subjective response to:

1. Medication.
2. Tolerance to activity, and/or:
3. Ability to work.

If the patient improved in one category, he was considered "fair." If improved in two—"good" and if they showed improvement in all—were considered an "excellent" result. When unpleasant sensations were produced by the stimulus—these disappeared when application of the electrical impulse ceased. No patient's condition was exaggerated by the technique.

Discussion

Unless there was an obvious discrepancy by objective appraisal in the patient's evaluation in respect to range of motion or residual tenderness, most of the above categories were accepted on the subjective appraisal.

An initial impulse might be to criticize the use of lumbar spine syndrome as a hap-hazard and un-scientific diagnostic group. It should be emphasized that many have had as many as ten exploratory laminectomies and/or repeat fusions. Almost all had back pain—stress related and ra-

diating leg pain. More specific diagnostic tests did not appear justified as further surgical treatment was not a realistic alternative.

All of the patients chosen had pain syndromes for periods varying between one and fourteen years; the low back syndrome patient underwent an average 3.5 surgical procedure.

The succeeding tables of the results of out-patient and in-patient appraisals are included.

Our results in out-patient settings indicate a higher percentage of satisfactory response to electrical stimulation then one would expect on merely a "placebo" effect.

A higher degree of effectiveness was exhibited while patients were hospitalized, but it was not possible to exclude the possible potentiating effects of an organized operant conditioning program.

Following application of transcutaneous electrical stimulation, improvement in pain would occur within the first few treatment sessions. Patients would soon learn to find the appropriate "trigger zones," impulse rate, intensity, and time of application. Few patients would seem to improve following the initial trial period of two weeks.

Improvement in most instances was sustained throughout most of the application program. In many instances the overall effectiveness was slightly diminished with time. This loss, however, was not significant enough to drop a patient from one category to an inferior category.

The significance of results are difficult to assess because of the lack of satisfactory objective guides and short span of the study. A "patient profile" is being developed to make these guides more accurate and meaningful.

Summary

This method appears to be useful for the relief of several types of pain seen in orthopaedic practice, particularly pain unrelieved by many surgical approaches.

This presentation offers electrical stimulation to the skin as an effective means for treating a wide variety of chronic pain syndromes in orthopaedics. The mode of action of this modality is not fully substantiated, but application of this technique to broader clinical trials and experimental work may answer many questions.

The criteria for patient selection have been difficult to establish. The present "selection" has been primarily the referral of prolonged and usually complex orthopaedic problems and in many instances the typical "unwanted patient."

There are no recognizable long lasting physiologic contraindications to the use of electrical stimulation and temporary undesirable or intolerable sensations produced by the stimulus will cease once the impulse has been stopped.

The untoward skin reactions have been minimized by the use of a tincture of Benzoin interface as well as a change to a carbonized rubber electrode. Superficial skin reactions respond quickly and have been completely reversed once the technique has been discontinued.

It is tempting to become enthusiastic with a technique that offers some relief in "hopeless or difficult" cases, but this study presents a relatively few number of patients and a relatively short follow-up period.

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Food Allergy in Atopic Dermatitis

Diagnosis of Food Sensitivity Using Patch Tests

WILLIAM E. WALSH, M.D., F.A.C.A.*

A method is described for the investigation of food allergy in atopic dermatitis. Fifteen patients were studied by 48-hour patch tests using foods and citric acid. In five patients the patch tests were positive and repeated challenge and avoidance trials showed that the positive-reacting foods caused the atopic dermatitis. The test is a helpful diagnostic tool in investigation of this difficult problem.

THE PATIENT WHO develops hives after eating fish or egg shows that foods can be allergens. In digestion, foods form non-allergenic amino acids, fatty acids and simple sugars, but digestion can be bypassed and intact allergenic food molecules absorbed into the body.[1] Immediate hypersensitivity, including hives and anaphylaxis, is the most intensively studied allergic food reaction.[2] Food ingestion also provokes delayed hypersensitivity. Matthews and Soothill have found indications that the complement system is activated in certain milk-sensitive patients challenged with milk.[3] May and Alberto observed lymphocyte proliferation, both in vitro and vivo, in cases of suspected food allergy after food challenge.[4]

Allergy to foods may be a causative factor in certain types of eczema that fit the patterns and history of atopic dermatitis.[5] Unfortunately, the routine allergy "prick" tests give little help in diagnosis; one must use diet manipulation in arriving at a diagnosis. In certain patients, dietary manipulation will isolate a food that repeatedly brings eczema with challenge.

The manifestations of atopic dermatitis share similarities with those of contact dermatitis; for example, rashes can look alike even if the location and history differ. Patch tests are very helpful in finding causes of contact dermatitis.[6] The dependence of contact dermatitis on sensitized lymphocytes leads to its classification as a disorder of delayed hypersensitivity.[7] If delayed hypersensitivity to foods is involved in the pathogenesis of atopic dermatitis in some patients, the diagnosis may yield to patch testing.

This study reports experience with food patch tests followed by challenge tests in patients with atopic dermatitis.

Materials and Methods

Selection of Patients

The patients were referred by primary physicians for evaluation and management of eczema.

Treatment began with training in the care of the skin and investigation of contact allergies. If eczema persisted and the pattern and history indicate atopic dermatitis, food patch tests were employed. Fifteen cases of atopic dermatitis were diagnosed and tested. Two patients were lost to follow-up. Seven patients had negative skin tests. One patient had complete clearing of eczema following a diet dictated by patch tests; his eczema did not return on challenge, and he is not included. Five patients had positive food patch tests, and avoidance and challenge allowed verification of results. Their cases are discussed.

Selection of Food Antigens

History and results of any previous dietary manipulation determined the selection of food antigens. As these patients were tested, the results were used to broaden the list of tested antigens and refine testing methods. Tests included whole milk, tomato juice, crushed corn kernels, cocoa, raw egg, and whole wheat flour, as obtained in local grocery stores. Citric Acid USP was used as a 10% solution in water. Other foods are used if the history suggests problems.

Application of Patch Tests

After cleansing the back with an acetone-alcohol solution, test materials were applied on a 1-cm non-stick Telfa® square and covered with an occlusive tape. Tapes were removed at 48 hours

*Clinical Instructor, University of Minnesota School of Medicine, Minneapolis.

and the area covered by the square outlined. Tests were read 30 minutes later and reevaluated in 24 to 48 hours. Grading was as follows: + for mild erythema, ++ for severe erythema, +++ for erythema and papules and ++++ for erythema, papules, and vesiculation.

Challenge

Each food was tested by a three day large-quantity feeding at each meal. The challenge was terminated if dermatitis flared. Citric acid challenge included citrus fruits and beverages with citrus flavoring.

Results

Food patch tests reacted positively in five cases. The patients are described below.

Case Reports

Case 1

Eczema developed at 14 months of age, varying in extent but often covering the whole body. His history indicated a definite wool contact dermatitis and probable reactions to animals and grass pollens. In spite of control of these contact allergies, severe eczema remained. At 22 months of age, patch tests yielded a ++++ reaction to corn, ++ to wheat, and + to milk. A diet eliminating these foods resulted in complete skin clearing in two months. Multiple challenge feedings demonstrated severe dermatitis with small corn, moderate wheat, and large milk ingestion. Repeat testing at three years of age gave the same results and questioning at that time showed that the pattern of food intolerance had persisted without noticeable change.

Case 2

Eczema appeared soon after birth and disappeared when cow's milk was replaced with a soy formula. Cow's milk was re-introduced at one year of age; eczema reappeared at an unspecified later time. The antecubital fossae were primarily involved, although the rash spread to the trunk and extremities in the winter. At nine years of age, after disappointing improvement with routine skin care, patch tests were employed and a ++++ reaction to milk resulted. On three occasions, avoidance of milk cleared the skin. Milk challenge caused the eczema to return.

Case 3

A fourteen year old girl complained of a chronic eczema of the antecubital fossae and forearms for the past 10 years. Routine skin care caused little improvement. Elimination diets implicated corn, wheat, and tomato juice. A patch test gave negative reactions to corn and wheat and a ++ reaction to citric acid. Corn and wheat challenge did not result in increased rash, but two citric acid challenges evoked severe dermatitis. Her skin cleared after institution of a citric-acid-free diet.

She was seen nine months later with a recurrence of her rash after a history of abandoning her citric-acid-free diet after three months. Two weeks after restricting the diet, her skin again cleared.

Case 4

Eczema developed at two months of age, at first covering her cheeks but later covering her whole body. In her teens, it moved to the hands and antecubital fossae. She was known to have a contact allergy to rubber. Wheat and corn patch tests were +. Two separate courses of challenge and elimination diets showed corn and wheat to be the cause of her eczema.

Case 5

This patient was seen for evaluation at twenty-five years of age. An eczematous rash appeared for one summer in infancy. At twelve years of age the rash returned, covering the whole body but worse on the face, neck, chest, and antecubital fossae. Contact allergy patch tests returned a ++++ reaction to formalin which may have been job-related, as he worked recapping tires. A + reaction to cocoa and ++ to citric acid and egg appeared on food patch tests. Separate challenges with citric acid and cocoa on two occasions resulted in marked skin eruption but he tolerated well-cooked eggs. Instruction in attempts to avoid formalin in his work, and avoidance of cocoa, citric acid, and egg have given almost complete skin clearing.

Comment

Of the fifteen patients tested for food sensitivity, five reacted positively to food patch skin tests. These results were reproducible on challenge feedings and chronic atopic dematitis receded or cleared completely when these foods were eliminated from the diet. Negative skin tests were also helpful; challenge with these foods did not provoke eczema even when previous dietary manipulation appeared to implicate them. The only exception was cocoa; several patients had negative tests but appeared sensitive to the ingestion of cocoa. These false negatives are unexplained.

The study gave some indication of the relative effectiveness of dietary manipulation and food tests. The diagnosis had been missed, although elimination diets had been tried at some time in each of the patients studied. Reasons for failure probably included the confusion caused when contact and atopic dermatitis coexist, or when more than one food causes dermatitis. Failure also results from the decreasing patient cooperation when the weeks of elimination and challenge necessary to test one food cumulate to the months needed to test several to many foods. Experience with these patients indicates the time necessary for diet studies: in Cases 1, 3, and 5 maximum skin clearing required two months, and repeated challenges required several more months before the diagnosis

was confirmed. Even with the diagnostic help of patch skin tests, the times required are long, but without this help the problem is magnified. Atopic and contact dermatitis coexist. In Cases 1 and 4, wool and rubber sensitivity appeared certain by history and Case 5 reacted vigorously to formalin. Contact-allergen testing combined with food testing allows the physician to diagnose this coexistence, and does not allow the persistence of one type of eczema to confuse the search for the other. A surprising finding of this investigation was the role of citric acid in atopic dermatitis. Patch tests were positive, and challenge and elimination diets supported the diagnosis. Citric acid, a small molecule normally found in the body, should not cause immunologic reactions. Perhaps an abnormal carrier-hapten complex or peculiar polymerization permits citric acid or a byproduct to become antigenic.[8] Alternatively, eczema may arise from a biochemical inability to handle the large amounts of citric acid found in some diets. Whatever the cause, further study is necessary.

Needing further study is the role of delayed hypersensitivity in atopic dermatitis. The response to patch testing is presumptive evidence for delayed allergy, but studies of antibodies and lymphocytes will be needed before more definite statements can be made.

Acknowledgment

Joseph R. Kelly, M.D. assisted in the investigation. Patients were referred by E. Dale Cumming, M.D., Samuel K. McHutchinson, M.D., and the staff of the Twin City Group Health Medical Centers. Eaton laboratories assisted in preparation of this manuscript.

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Cover Photo

"Breath of Spring"

The photograph on the cover was taken on a May morning at the home of Dr. Charles W. Jarvis in White Bear Lake. The Eastern Columbine *(Aquilegia Canadensis),* every bit as showy as its more famous western cousin, is one of the easiest of wildflowers to grow in the home garden. It thrives in an environment of light shade and friendly neglect.

Dr. Jarvis is the pathologist at St. Paul Children's Hospital. His hobbies include back-packing and wild life photography. This picture was taken on Kodachrome II film through a Macro Takumar lens. Dr. Jarvis also edits the "Laboratory Medicine" section of MINNESOTA MEDICINE, a monthly feature of the journal.

Pediatric Day

May 17, 1975

"Pediatric Day sponsored by the Mayo Clinic-Mayo Foundation and arranged for by the Department of Pediatrics will be held May 17, 1975. The Amberg-Helmholz Lecture, a feature of Pediatric Day will be given by Chester M. Edelmann, Jr., M.D., Professor and Chairman, Department of Pediatrics, Albert Einstein College of Medicine. Presentations dealing with problems which occur in the practice of Pediatrics will be made by members of the staff of the Mayo Clinic and the faculty of the Mayo Medical School from the Departments of Pediatrics, Orthopedics, Surgery, Neurology, Cardiology, Radiology, and Psychiatry. For information, write Dr. E. C. Burke, Program Director, Mayo Clinic, Rochester, Minnesota 55901."

Bone Imaging

JAMES R. CUSTER, M.D.;* REX B. SHAFER, M.D.;* and MERLE K. LOKEN, M.D. Ph.D.*

The ease of preparation of such radiopharmaceuticals which deliver a low total body radiation dose has revolutionized bone scanning and has relegated ^{85}Sr and comparable agents to the past history of bone imaging.

THERE HAS BEEN increasing interest in bone imaging with the advent of the gamma scintillation camera and the use of technetium compounds for liver, brain, and lung imaging. The utility of recognizing bone pathology, especially metastatic disease, stimulated interest in research and development for more ideal bone-seeking nuclides. It had been demonstrated that more than 50% of bony architecture may be destroyed before roentgenograms became positive, while bone scans revealed abnormal areas of increased uptake much earlier in the disease process.[1] Unsuspected bone metastases have been discovered in patients with primary malignancy, yet poor resolution was a serious handicap in the diagnostic evaluation of patients.

Radiopharmaceuticals (Table 1)

Until recently, research on bone imaging using radionuclides emphasized development of nuclides with chemical and metabolic activity similar to the constituents of bone crystal. Through ion exchange, the isotopes of Calcium (^{45}Ca, ^{47}Ca), Strontium (^{85}Sr, ^{87}Sr), and Fluorine (^{18}F) are incorporated into the bone hydroxyapatite crystal, enabling images to be obtained with appropriate detection equipment.

Many of these radionuclides are high energy gamma emitters. Hence, the majority of them pass through the crystal of a scintillation camera without interaction, accounting for a low detection efficiency with this instrument. Their physical half-lives are either very short precluding adequate time for preparation and administration, or very long causing the radiation dose to be excessive.

The ideal radionuclide for bone imaging should emit a single photon of moderate energy for use with the gamma camera (100-200 Kev), have a short physical half-life and a long shelf-life (long-lived parent), rapid uptake by bone of a significant fraction of the injected dose, insignificant

*Departments of Nuclear Medicine, University of Minnesota and Veterans Administration Hospital, Minneapolis, Minnesota.
Reprint requests to: Rex B. Shafer, M.D., Nuclear Medicine Service, Veterans Administration Hospital, 54th Street and 48th Avenue South, Minneapolis, Minnesota 55417.
See editorial, page 325.

TABLE 1
Agents*

Nuclides	^{47}Ca	^{85}Sr	^{87m}Sr	^{18}F	^{99m}TC-P Complexes
Half-life	4.53 da	64 da	2. 83 h	1.83 h	6 h
Decay	B^-	EC	IT	B+	IT
Gamma E (Kev)	1310 (74%)	514	388 (78%)	511 (annihilation)	140
Chemical form	chloride	nitrate chloride	citrate chloride	sodium salt	(see notes)
Dose (uCi)	50-100	50-100	250-1000	1000-2000	15 mCi
Time before scan	2-7 da	2-7 da	1 h	2 h	2 h
		Radiation dose (millirads)			
Bone	2100-4200	1500-4500	25-100	120-360	800
Whole body	150-300	350-700	5-20	35-70	200
Patient preparation		cleanse bowel	empty bladder	empty bladder	empty bladder
Comments	High-energy gamma	Long scan period	From generator ($^{87}Y, T_{1/2}$, 80 h)	Proximity to production site	

*Adapted from Kniseley, RM, Andrews, GA, et al.: Bone marrow and skeletal scanning. Radiol. Clin. North Am. VII: 265, 1969, by permission.

fecal excretion, low radiation dose to the body, and be available in a sterile and pyrogen-free form at reasonable cost.

Because calcium is a normal constituent of the hydroxyapatite crystal of bone, it should be an ideal nuclide for studying bone metabolism. However, ^{45}Ca is a pure beta emitter and therefore cannot be detected by gamma imaging devices. Another radioisotope of calcium, ^{47}Ca, emits a gamma ray of 1.3 Mev which cannot be effectively collimated by either a gamma camera or rectilinear scanner.

The radionuclide most widely used in the past was ^{85}Sr which has a long physical half-life (65 days) and emits a gamma ray of 0.51 Mev. Because of a long biological half-life in addition to the long physical half-life, the usual maximum administered dose was 100 microcuries which provides less than an ideal photon flux for imaging. In addition, the very high energy prevents efficient detection particularly with gamma camera devices. ^{85}Sr is slowly excreted through the bowel. The slow clearance necessitated a delay of more than two days between administration and subsequent scanning. In addition, it was necessary to cleanse the bowel thoroughly in order to adequately visualize Strontium uptake in the pelvic portion of the skeleton.

The radioisotope of Strontium, ^{87m}Sr, with a short physical half-life of 2.8 hours has been used. This nuclide is obtained from a generator system containing the parent radionuclide, 87-Ytterium (^{87}Yt). Relatively large quantities of ^{87m}Sr could be given because of the short physical half-life. However, the blood clearance is relatively slow and consequently a significant blood background exists at the time that scans are obtained.

18-Fluorine has achieved some popularity but because of its short physical half-life of 1.8 hours it has been generally available only to those investigators near the production site. This radionuclide is produced in a cyclotron and emits positrons with subsequent annihilation radiation of 0.51 Mev. This agent has been used most successfully with dual-headed scanning devices because of the relatively high detection efficiency for the thick crystals in this unit. ^{18}F is cleared from the blood relatively rapidly so that the tissue background is relatively low and adequate visualization of the skeleton can be obtained.

Because none of the usual bone seeking radionuclides possessed ideal characteristics for bone scanning, investigations were carried out using alkaline earth and rare earth radionuclides.[2,3] These include radioisotopes of the rare earths-Dysprosium (^{157}Dy), Samarium (^{153}Sm), Erbium (^{171}Er), Lutetium (^{176m}Lu, ^{177}Lu), and the alkaline earth series: Calcium, Strontium, Barium and Radium. Just as Radium is a bone-seeker, so is Barium-135m and Barium-131 (^{135m}Ba, ^{131}Ba). Gallium isotopes (^{68}Ga, ^{67}Ga) have also been used. High doses of ^{68}Ga saturate plasma protein binding sites with subsequent substitution for calcium in newly-formed bone.[4] ^{67}Ga deposits in a variety of malignant neoplasms probably through protein binding.[5] All these nuclides were either too expensive or impractical to produce, could only be given in very small dose because of equivocal biological safety or had less than ideal physical characteristics.

Technetium

A very popular radionuclide in the practice of Nuclear Medicine today is ^{99m}Tc (pertechnetate) which emits a gamma ray of 140 Kev. Because of its metastable status, no particulate emission is present. Its short physical half-life of six hours permits large quantities to be administered without significant radiation dose to patients. Because of unique multivalent properties of technetium, it may be attached chemically to many agents such as proteins and other organic or inorganic molecules without substantially altering their basic structure.[6]

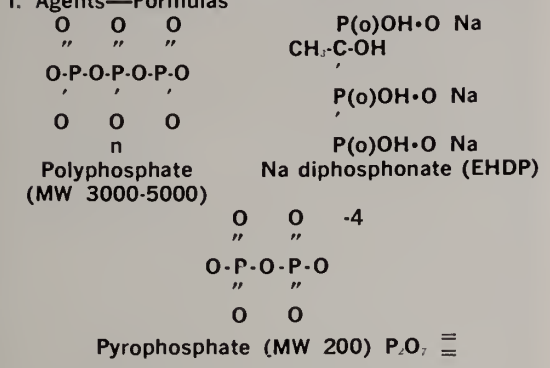
Using the chemical properties of technetium, Subramanian investigated the use of ^{99m}Tc-polyphosphate complexes for skeletal imaging.[7,8] His approach followed the rationale known for many years that anion complexes localized in bone and that technetium readily formed this type of complex. The exact mechanism of localization of a technetium complex such as this in bone is not known although it has been found to be dependent on regional bone blood flow.

Following the studies of Subramanian, other technetium compounds have been found to be quite useful, i.e., pyrophosphate and diphosphonate (Table 2).[9-12] These latter agents have been reported to provide better stability *in vivo* and a more rapid blood and renal clearance than polyphosphate. In addition, they appear to be somewhat easier to prepare chemically.

Using autoradiography, ^{99m}Tc-polyphosphate

TABLE 2
^{99m}Tc Compounds for Skeletal Imaging

I. Agents—Formulas



complex has been shown to localize by absorption on bone surfaces and on interfaces between older and newer bone.[13] Although different in chemical composition and molecular weights, the three phosphate compounds are cleared rapidly by the kidneys and extracted by the bone within one to three hours. Doses of 15 mCi may be given, more than five times that of ^{18}F and 150 times that of ^{85}Sr. Rapid bone uptake and renal extraction of blood levels permits scanning to be performed two to four hours after injection. Hydration of the patient to insure good renal clearance is the only preparation necessary. All three compounds are currently being used in our department and give excellent results.

Instrumentation

As indicated in the previous section, both rectilinear scanners and scintillation cameras have been used for bone imaging. Rectilinear scanners are the instruments of choice when high energy gamma emitters are used because of the higher detection efficiency. In addition, total body images are obtained with dual probe scanners (Figure 1). When radionuclides of relatively low gamma energy are available, scintillation cameras can be used effectively. As a stationary imaging device, the camera is relatively easy to use. In addition, the data are readily recorded using either videotape or computer devices. Computer analysis of data permit quantitative information on regional bone uptake of selected radionuclides.

Clinical Application

Uptake of the isotope depends upon the metabolic activity of bone (osteoblastic activity) and the presence of a vascular supply to carry the



Fig. 1—Normal whole body scan in anterior and in posterior views.

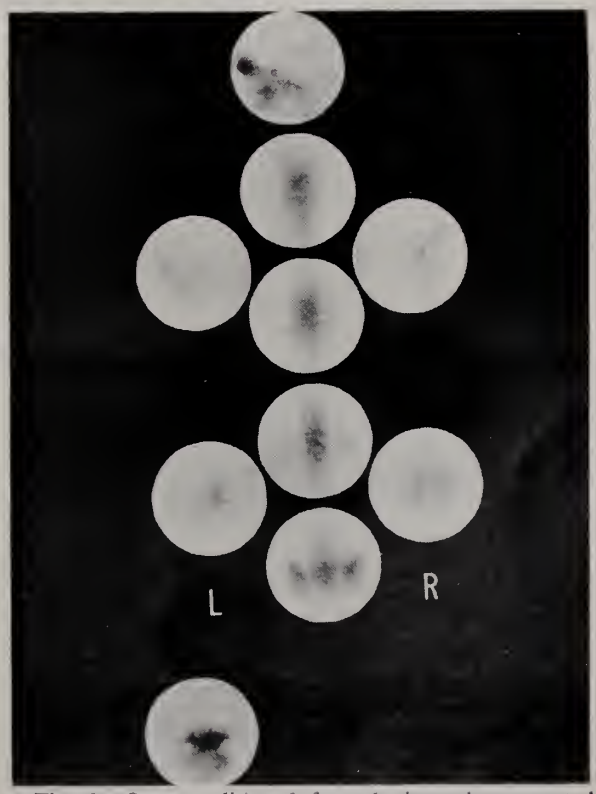


Fig. 2—Osteomyelitis of frontal sinus demonstrated prior to x-ray changes. Note frontal view lower left.

isotope to the bone. Both ^{18}F and ^{85}Sr are similar to calcium in that they localize in the skeleton and reflect the metabolic activity of the bone by exchanging with the ions of the hydroxyapatite crystal. When tumors elicit osteoblastic activity, increased ion exchange or absorption of isotope in the reactive new bone becomes possible and detection can be performed. Tumors lacking osteoblastic response may be detected if the regional blood flow at the site is increased to allow increased nuclide deposition.

Initial application of bone-imaging radioisotopes was the detection of metastatic disease.[14,15] Other uses for bone-seeking nuclides have been reported, including the early detection of osteomyelitis (Figure 2),[16] determination of age of vertebral fractures,[17] localization of biopsy sites, differentiation of bone islands from metastases, definition of portals for radiation treatment, and monitoring the effect of therapy on the course of disease.[18,19]

Currently in our department, bone imaging is used to detect primary and metastatic bone disease (Figures 3, 4, 5) and to stage malignancy especially carcinoma of the lung, breast, thyroid and prostate (Figure 6) before radical therapy is instituted, and whether or not the patient has symptoms referable to the skeletal system. The excellent images obtained are also useful in assessing causes of unexplained bone pain, and high alkaline phosphatase levels, and in cases of metabolic bone disease.

Recognition of the extent of Paget's disease of bone is important as new treatment modalities become available (Figure 7). Since Paget's disease is a disease of over-production of uncalcified osteoid, "lucent" areas seen on Xray are more metabolically active than "sclerotic" areas. Therefore, the radioisotope bone scan becomes positive earlier in the disease than radiographs and can become normal later in the disease when the Xrays show extensive, dense skeletal involvement. It has been found that the urinary hydroxyproline level and the serum alkaline phosphatase level correlate with the percent of skeletal involvement. The bone scan detects clinically-active lesions more frequently than do radiographs. Both scans and radiographs are considered necessary and complimentary in the evaluation of skeletal involvement in patients with Paget's disease.[20]

Rheumatoid and degenerative arthritis (Figure 8) and septic arthritis give positive scans depend-

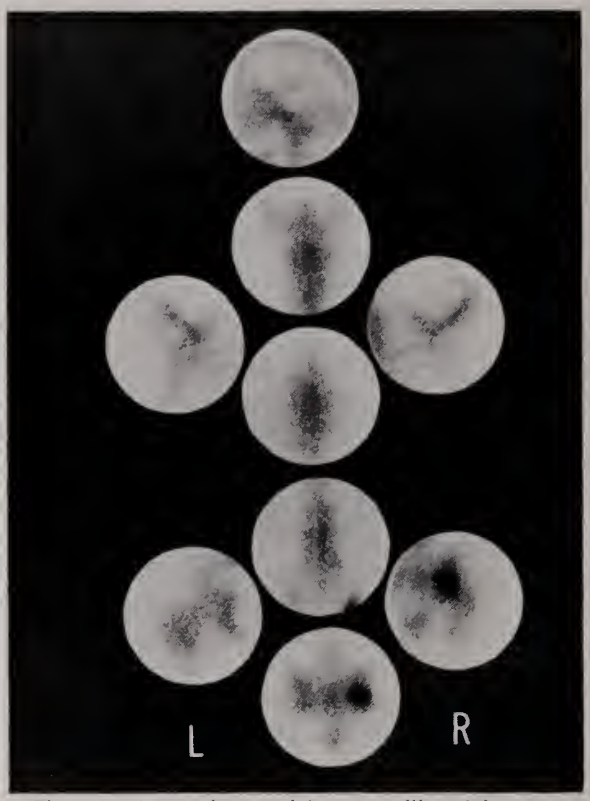


Fig. 3—Metastasis to right sacro-iliac joint (x-ray negative).

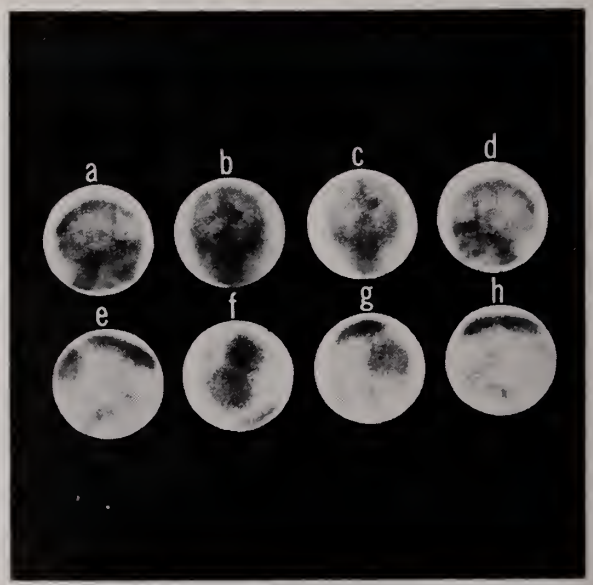


Fig. 4—(a-d) Occipital uptake at pressure point from prolonged recumbency. (e-h) Calvarial metastases from thymoma. a,e: Right lateral; b,c: Posterior; f: vertex; g: Anterior; d,h: Left lateral.

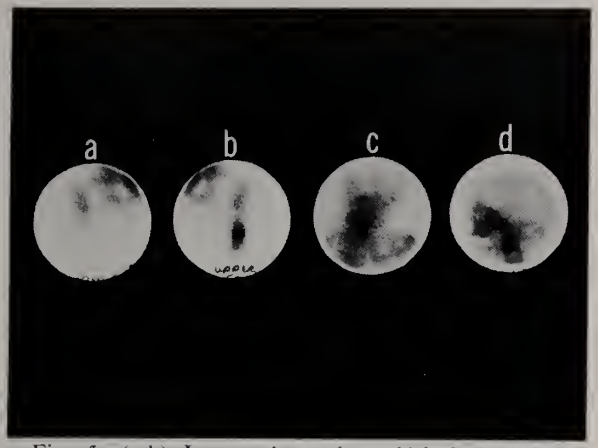


Fig. 5—(a-b) Increased uptake midshaft left femur due to lymphosarcoma; right side (a) negative. (c-d) Abnormal activity in cervical region in patient with spondylosis.

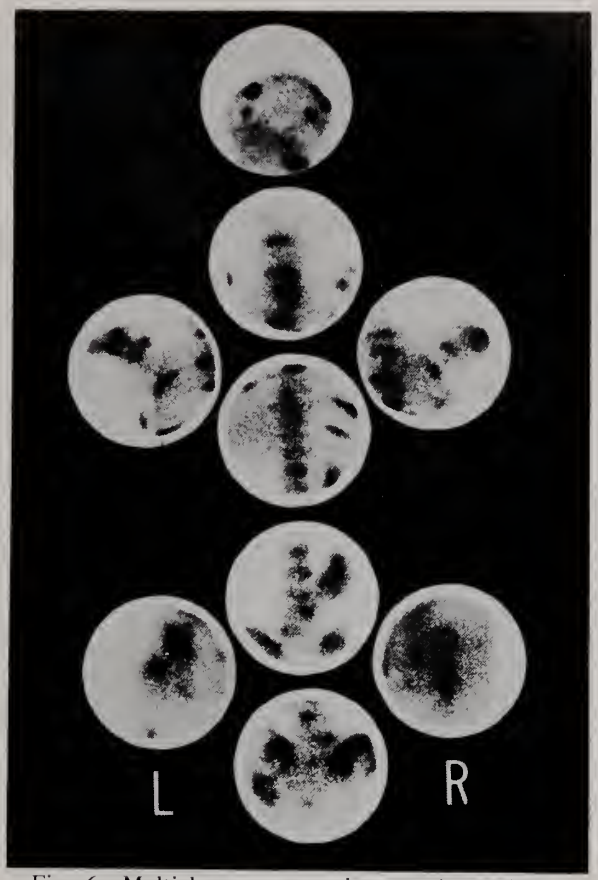


Fig. 6—Multiple metastases in a patient with carcinoma of the prostate. Note absence of left kidney and hydronephrosis of right kidney.

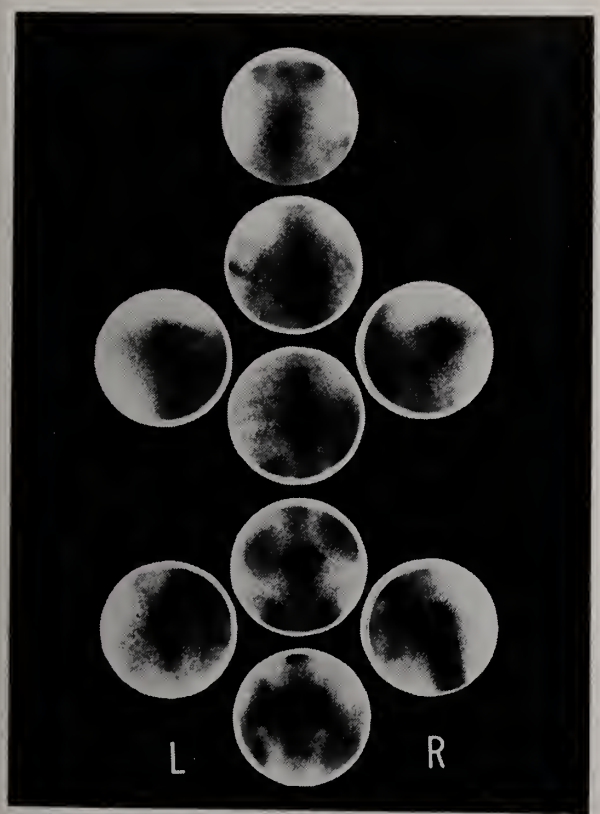


Fig. 7—Paget's disease involving right femur, pelvis, lumbar and thoracic spine.



Fig. 8—Increased activity in rheumatoid arthritis best seen at the M-P joints of both hands and the right foot.

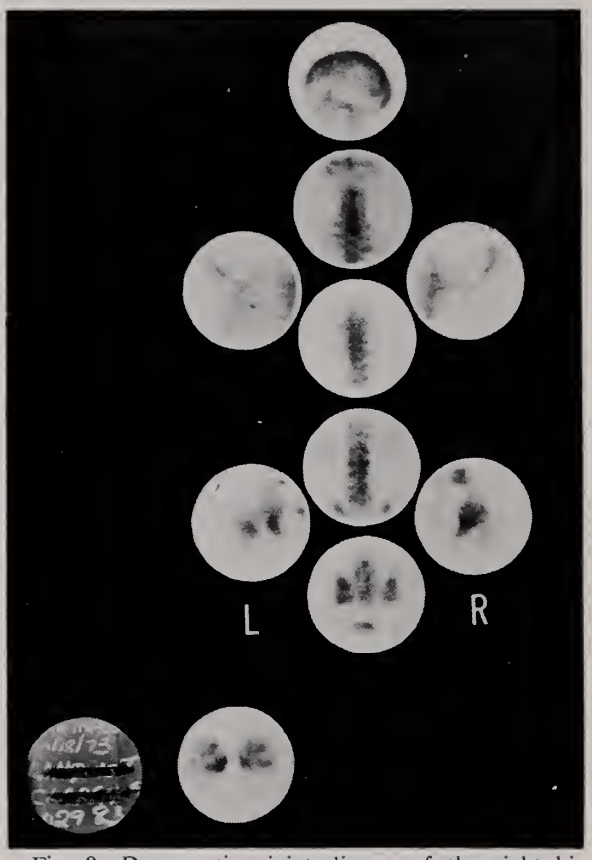


Fig. 9—Degenerative joint disease of the right hip and left knee. Increased activity in left sacro-iliac joint secondary to stress.

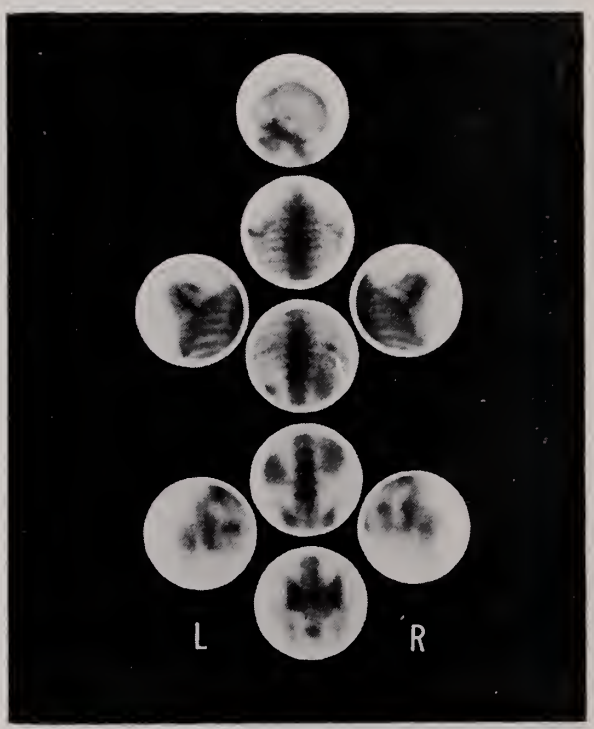


Fig. 11—Fracture seven years prior of right ninth rib still showing increased activity; otherwise negative.

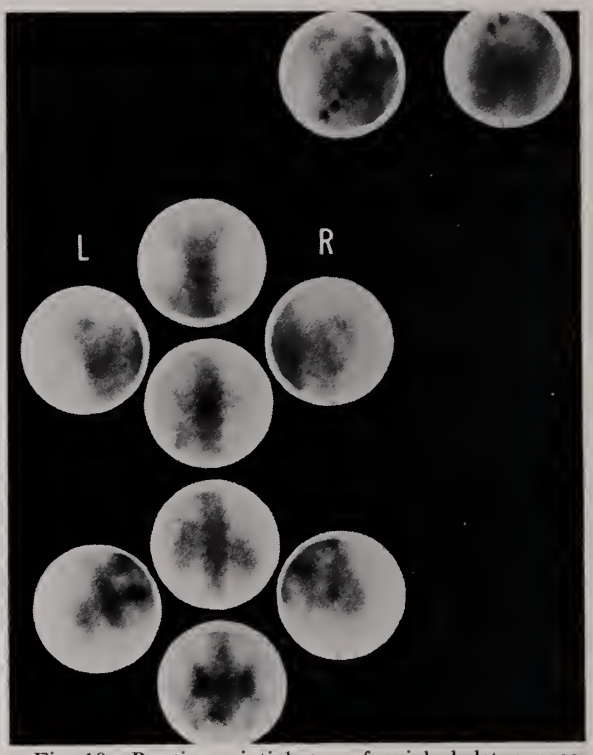


Fig. 10—Routine scintiphotos of axial skeleton negative. The patient complained of right anterior rib pain with special views (upper right) showing increased uptake in multiple rib fractures.

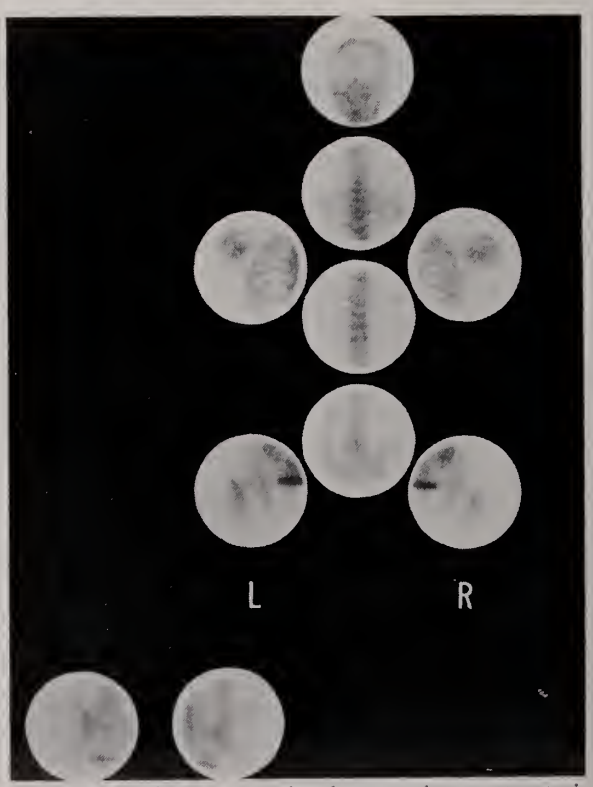


Fig. 12—Diffuse bone involvement by mastocytosis with unremarkable study due to diffuse bone involvement and lack of reactive new bone.

ing on the degree of reactive bone activity. Questionable lesions on roentgenograms can often be resolved by the bone scan.

Interpretation and Pitfalls

Normally, increased activity is seen in areas of active bone metabolism and vascularity: ends of long bones, acetabulae, sacro-iliac joints, iliac crests and in pressure points due to prolonged recumbancy (spine of scapula, occiput, upper sacrum) (Figure 4).

Degenerative disease of the spine and fractures will show marked increased uptake of radionuclide and may be confused with metastases unless radiographs are available for comparison. This is particularly true with rib fractures as they show increased activity for many years (Figures 5, 9, 10, 11).

Abnormal areas are usually manifest as asymmetric foci of increased activity. Joints and long bones can be compared to those on the opposite side. Similarly, one side of the ribs, pelvis and calvarium can be related to the other. For midline structures such as the spine, radioactivity in a vertebral body in question may be compared with that seen in bodies immediately above and below the questionable area.

Because uptake of bone scanning radioisotopes is not specific for malignant disease, there must be dependence on the physical examination, on other clinical information, as well as an evaluation of the patient's Xrays prior to scan interpretation. Diffuse bone involvement may be missed (Figure 12) as can highly anaplastic tumors, multiple myeloma and reticulum-cell sarcoma due to the lack of reactive bone.

Conclusion

The search for elements which were metabolically similar to calcium in their uptake in the bone hydroxyapatite crystal has been abandoned in favor of a more empirical approach which exploits the nearly ideal physical and chemical properties of ^{99m}Technetium. This radionuclide forms complexes with multiple compounds. It is labeled to phosphorus containing molecules to form a bone-seeking radiopharmaceutical which may give superior images of bony anatomy.

Acknowledgments

Special thanks to Eileen Dahlberg and Kathy Guttormson for typing of the manuscript and to Dr. John Wolff for his assistance in reviewing the cases.

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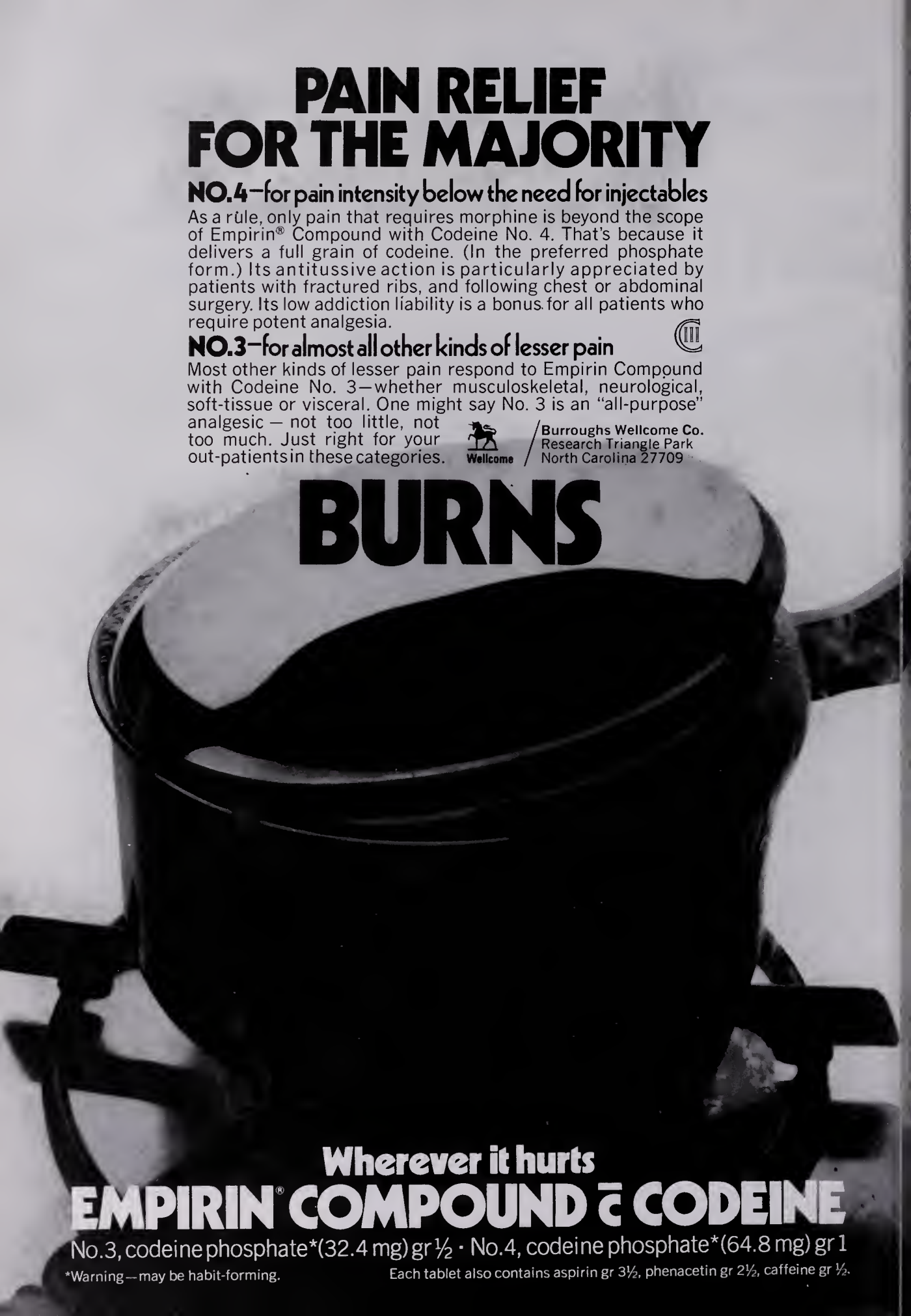
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Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

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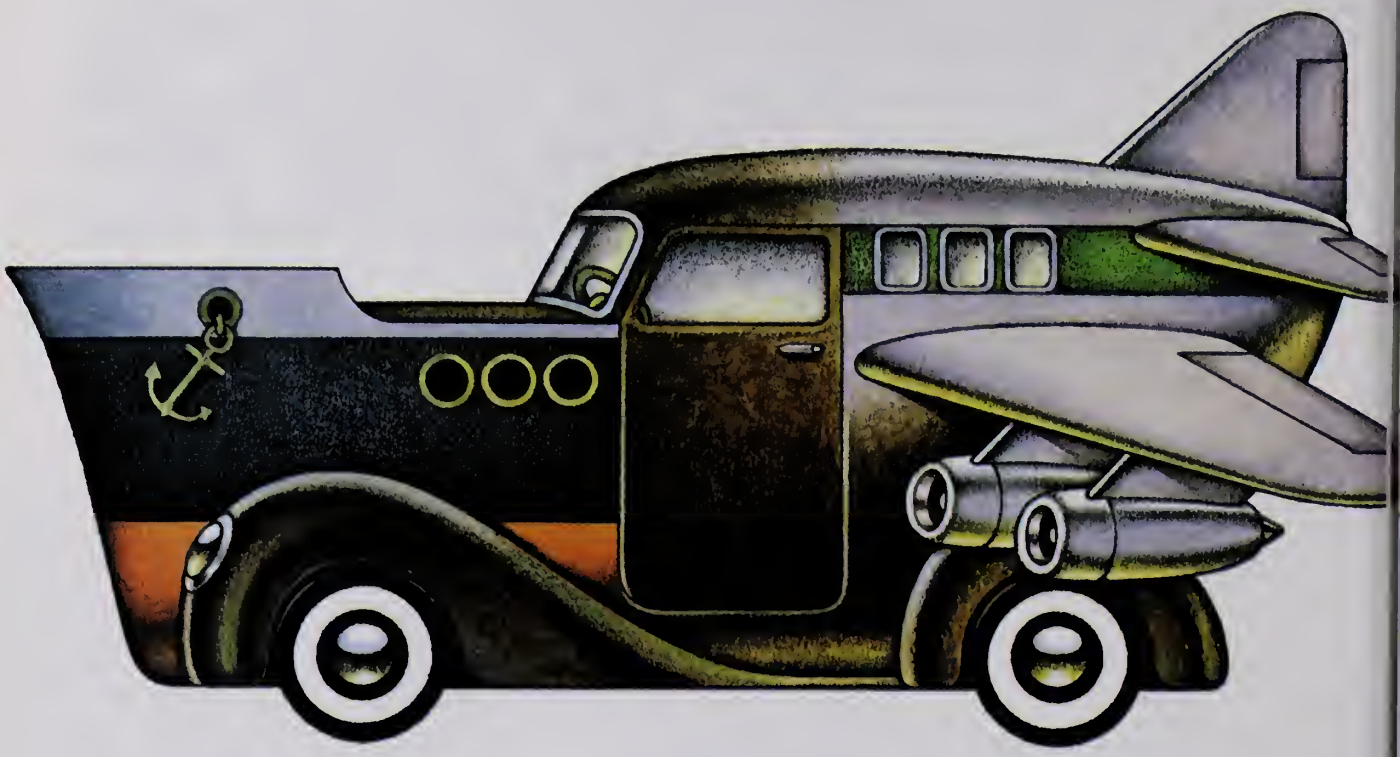
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Meclizine HCl is contraindicated in individuals wh have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occu with use of this drug, patients should be warned of this pos sibility and cautioned against driving a car or operatin dangerous machinery.

Usage in Children: Clinical studies establishing safety an effectiveness in children have not been done; therefor usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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Editorials

Bone Scanning*

NUCLEAR MEDICINE represents one of the newest and most rapidly expanding areas of present day medicine. This field results from the convergence of a wide variety of clinical and scientific disciplines. Thus, its practitioners include as many physicists and mathematicians as it does pathologists, radiologists, and internists. Perhaps it is because of this diversity of backgrounds that this relative newcomer on the medical horizon is developing from the puny infant of 20 years ago to the lusty adolescent of today.

The field of Nuclear Imaging came into existence during the early 1950s. Many radionuclide tracer studies had been performed during the previous several decades, but it was not until June of 1946 that radioactive isotopes were made available for public distribution from Oak Ridge and subsequently from Brookhaven National Laboratory. Taking advantage of this new supply, together with several major advances in nuclear engineering, Benedict Cassen developed an instrument by which the distribution of radioactivity in an organ could be pictorially represented. This he named the rectilinear scanner. Thus, for the first time, it became possible to graphically display the regional function of an organ, and not merely its anatomic structure as was obtained with conventional radiography. Since the first rectilinear scanner was introduced in 1951, this instrument has become one of the mainstays of clinical nuclear medicine and many thousands of instruments embodying Cassen's principles are to be found working throughout the world. Another approach to the pictorial recreation of radioactivity distribution is that embodied in Anger's gamma camera, the first example of which was demonstrated in 1958. In the relatively brief period of two decades, instrumentation design has advanced to the stage that both the rectilinear scanner and the Anger camera are each capable of identifying lesions of approximately 1 cm. in diameter.

Equally impressive gains have been achieved in the field of Radiopharmacy. The earliest tracer studies of the skeletal system were performed with phosphorus, calcium and strontium. It was not, however, until 1961 that radionuclide bone scanning was introduced by Fleming, et al. These workers showed abnormal accumulation of 85-Strontium in areas of increased osteoblastic activity. In more recent years, this agent was superceded by 87m Strontium, by 18 Fluorine and by the ^{99m}Tc-phosphate complexes. These latter agents represent a very major advance over their predecessors. The combination of shorter physical half-lives which are measured in hours rather than weeks or months, together with the absence of primary beta-irradiation, results in substantially reduced radiation exposure to the patient and at the same time enables considerably higher doses of radionuclide to be administered. Thus, substantially improved statistical image quality is possible, together with considerably lessened radiation exposure. The practical result is that a scan of the entire skeleton may be performed in less than one hour with a radiation dose to the skeleton of approximately 675 mRad. With previous agents, the rather substantial radiation exposure restricted the use of bone scanning to those patients with tissue proven diagnosis of malignant disease. The reduced exposure produced by fluorine and the technetium complexes removes this restriction so that the bone scans may be ordered for the investigation of non-malignant disease processes or where there is only a sus-

See page 313.

picion of neoplasia. Thus, the number of patients who may potentially benefit from the bone scan has been greatly increased.

The strength of the bone scan techniquc is its ability to pictorially portray the osteoblastic activity throughout the skeleton. No other study as clearly shows that bone is, indeed, a metabolically active tissue, reacting to stress, trauma and destruction with an active repair process. It is this ability of the bone scan to identify and localize increased osteoblastic activity that makes it such a powerful and sensitive tool in the identification of skeletal abnormality. This technique is now widely regarded as the most sensitive method for the detection of focal skeletal abnormality. Thus, it is a very common experience for a metastatic deposit to become apparent on the bone scan either weeks or months before a change is apparent on the radiograph. It is estimated that between 30 and 50% de-mineralization is necessary before a lesion can be detected on Xray.

It is necessary, when interpreting a bone scan, to remember that, while this technique is the most sensitive currently available, it is also extremely nonspccific. This latter observation has major import in the interpretation of the bone scan. An area of focally increased radionuclide accumulation is no more than a reflection of locally increased osteoblastic activity in that area. The bone scan is unable to identify the underlying mechanism, and so, is unable to distinguish the disease process responsible for this change. Thus, the bone scan is an extremely useful tool in the distinction of the patient with a normal skeletal system from the patient with focal bone disease. Currently, a negative bone scan represents the most definite evidence for absence of localized bone disease, being substantially more sensitive in this regard than conventional radiography. On the other hand, an area of focally increased radionuclide accumulation in the bone scan indicates locally elevated osteoblastic activity in that region. The appearance of the scan may well be similar whether the underlying lesion is neoplastic, inflammatory or traumatic.

In summary, in the brief period of its existence, the discipline of Nuclear Medicine has provided a tool for the identification of bony disease which is unrivaled in sensitivity by any other currently available methodology.

Nicholas G. Nolan, M.D.*
Rochester, Minnesota

*Mayo Clinic, Mayo Medical School, Rochester.

Genetics of Psoriasis *

A FAMILIAL PATTERN of psoriasis has long been recognized by clinical and statistical studies. This pattern suggests a role for genetic factors in psoriasis. Studies of family pedigrees[1,2] have implicated a pattern of autosomal dominant inheritance with incomplete penetrance. The studies of Watson and coauthors[3] support the hypothesis that psoriasis is a hereditable disease and that it is determined by multifactorial inheritance. Multifactorial inheritance implies that multiple genetic and environmental factors are necessary for the expression of this trait as a clinically recognizable disease. This contention is supported by two facts: (1) a higher concordance rate for psoriasis among monozygous than among dizygous twins and (2) the significantly higher frequency of psoriasis among relatives of probands than among relatives of nonpsoriatic spouses of the probands.

Another interesting genetic observation is the association of certain antigens of the major histocompatibility locus in man (HL-A) with psoriasis. Russell and coworkers[4] studied the HL-A phenotypes of 44 Caucasian psoriatic patients from the Midwest and reported the presence of HL-A13 and possibly W17 in a statistically significant number of patients. White and coinvestigators[5] confirmed the increased frequency of HL-A13 and W17 in 156 Caucasian psoriatic patients and reported a decreased frequency of HL-A12. The W17 genetic marker characterized a subgroup of psoriatic patients with a high rate of affected relatives and slightly earlier age of onset. Subsequent study of a larger sample by the same investigators confirmed the high statistical significance of HL-A13 and W17 but not the decreased HL-A12.

Although the exact significance of these findings is not known at this time, it does provide an explanation for the flares of acute guttate psoria-

*See page 813, October issue, MINNESOTA MEDICINE.

sis following streptococcal infections, as a protein from group A beta-hemolytic streptococci has been shown to cross-react with certain HL-A antigens. The findings of HL-A phenotypes in psoriatic patients may provide insight into successful therapeutic regimens, crossreactivity to antigenic determinants related to provocative agents, or a perturbation in cellular regulatory mechanisms associated with HL-A.

Roy S. Rogers III, M.D.*
Rochester, Minnesota

*Department of Dermatology, Mayo Clinic and Mayo Foundation.

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Nephrotic Syndrome

BURKE AND ASSOCIATES in the January issue,* have successfully managed to synthesize a broad spectrum of clinical and pathologic detail about the complicated subject of the nephrotic syndrome. Their task has been simplified by the fact that the combined experience of these authors in the area of glomerular disease is unsurpassed and their expertise is widely recognized. The review begins with the minimal or nil lesion which has been an enigma to the clinician and pathologist alike as a cause of the nephrotic syndrome. It has become apparent through careful follow-up and repeated renal biopsies that characteristic glomerular alterations do occur in patients who do not respond to therapy as expected. Following a discussion of membranous and membranoproliferative glomerulonephritis, the authors end the review on a strong pathophysiologic note with structural-functional correlations.

Louis P. Dehner, M.D.†
Minneapolis, Minnesota

*See page 30.
†Associate Professor of Laboratory Medicine and Pathology, University of Minnesota School of Medicine.

Annular Pancreas in the Adult

THE REPORT BY Olin and Norum* in the March issue reminds us to consider annular pancreas in the differential diagnosis of duodenal obstruction —especially obstruction beyond the first part of the duodenum where peptic ulceration is rare. This embryological anomaly is of particular interest since it more often manifests itself after childhood, usually with the picture of duodenal obstruction, peptic ulceration due to stasis, or more rarely obstructive jaundice. The authors correctly stress that pancreatic division is not advisable in the majority of cases and that bypass is indicated. No mention is however made of duodenoduodenostomy or duodenojejunostomy of the Roux-en-Y type—procedures that should be considered. Vagectomy should not be a routine following gastroenterostomy, especially if no hypersecretion is present. Similarlarly antrectomy is not indicated in the uncomplicated case.

Grammatically, it should be noted that atresia is always congenital—thus duodenal atresia does not occur in adults—the fibrous duodenal obliteration should not be termed atresia.

Jonathan A. van Heerden, M.D.
Rochester, Minnesota

*See page 248.

Letter to the Editor

Dear Editor:

May I submit a historical note to the article by Drs. Haley and House, "Recurrent Anterior Dislocation of the Shoulder: Surgical Repair with a Modified Bristow Procedure" in the November, 1974, issue.*

At the 25th Annual Meeting of the Russell A. Hibbs Society, held in Bermuda in June of 1972, Sir Harry Platt, of Manchester, England, discussed a paper by Dr. Cline Hensley of Wichita, Kansas, "Transfer of Coracoid: Bristow Procedure, and Recurring Dislocation of the Shoulder." Platt stated that Bristow, who had been a close associate, had never discussed the operation to which his name was attached and that he was mystified by the rather anomalous development of this enponymic procedure. Subsequently, this mystery led me to question Arthur J. Helfet, Cape Town, South Africa, the man recognized for publicizing the coracoid transfer about Sir Harry Platt's statement.

In a conversation on the evening prior to my delivery of a paper on the Bristow procedure at the 1973 British Orthopaedic Association Meeting in Bristol, England, Arthur Helfet informed me that indeed Bristow had never performed the operation which had subsequently been ascribed to him. Helfet, upon completion of his training in Liverpool, moved on to London in the 1930's in association with Bristow and there discussed the concept of the coracoid transplantation with his friend. Bristow himself never performed this procedure but in 1958, to honor and memorialize his mentor, Helfet described the operation and submitted the manuscript using the term, "Bristow Procedure" in the title, Sir Reginald Watson Jones, as Editor of the British edition of the Journal of Bone and Joint Surgery, was opposed to eponyms and insisted upon the manuscript's publication as "The Coracoid Transplantation for Recurrent Dislocation of the Shoulder." Helfet related to me that he accepted this editorial modification but insisted upon rewriting the first paragraph in a fashion that was sufficiently ambiguous to lead the reader to surmise that the operation had in fact been devised by Rowley Bristow.

In the conclusion of my address to the British Orthopaedic Association, I suggested that in fairness to its originator and in deference to his wishes that Rowley Bristow be memorialized, that the procedure be henceforth known as the Bristow-Helfet repair for recurrent dislocation of the shoulder.

William J. Kane, M.D., Ph.D.
Ryerson Professor and Chairman
Department of Orthopaedic Surgery
Northwestern University

*See page 882, November issue, 1974.

Letters to the Editor

We would like to encourage physicians to contribute to the Letters to the Editor Section. We want to hear what you have to say, what you think, why you hold certain opinions. In short, we want to make this as lively and spirited a section as possible.

The Editors

Laboratory Medicine

Creatine Phosphokinase Isoenzymes and Myocardial Infarction

THOMAS O. SWALLEN, M.D.*

THERE IS GROWING INTEREST in creatine phosphokinase (CPK) isoenzymes as a diagnostic aid in assessment of acute myocardial infarction. This intensified interest derives from two conditions. One is the recent development of sensitive and relatively easy procedures for detection of CPK isoenzymes. The other is the need for improved specificity, and speed in establishing the diagnosis of acute myocardial infarction.

Measurement of total serum CPK has been used for many years in diagnosis of myocardial infarction. Experience has shown, however, that total serum CPK may be increased in disorders other than myocardial infarction, including pulmonary embolism, intramuscular drug injections, hypothyroidism, strokes, following exercise, cardioversion and surgical trauma. Some of these conditions may mimic or be associated with myocardial infarction, causing diagnostic difficulties. Isoenzymes of CPK may provide a way of avoiding these difficulties.

Three isoenzymes of CPK have been identified. Each is a dimer, composed of two subunits, M or B. CPK, therefore, exists as MM, MB, or BB forms. These isoenzymes may be separated by electrophoresis or by ion exchange column chromatography. Skeletal muscle contains only the MM isoenzyme. Brain contains only the BB isoenzyme, while heart muscle contains both the MM and the MB isoenzymes.

Normal individuals have only the MM isoenzyme in their serum, presumably derived from normal turnover of skeletal muscle cells. Serum of patients with recent myocardial infarction contains the MB isoenzyme as well as the MM isoenzyme. The MB isoenzyme appears within two to six hours after the infarct, and persists in serum for 24 hours or longer. Studies by a number of workers[1-3] indicate that virtually all patients with myocardial infarction release detectable amounts of the MB isoenzyme into their serum. Patients with other conditions which may cause signs and symptoms suggestive of infarction, including angina pectoris, pulmonary embolism, and congestive heart failure, do not have serum MB isoenzyme. Also, the MB isoenzyme is not seen in patients following surgical trauma, cardioversion, after exercise, or after intramuscular drug injections. Thus, CPK isoenzymes serve to bring an enhanced measure of specificity to the diagnosis of acute myocardial infarction.

There are a few conditions other than myocardial infarction in which the MB isoenzyme has been found in serum. These include some patients with hypothyroidism, some with muscular dystrophy, polymyositis and dermatomyositis, malignant hyperthermia, and carbon monoxide poisoning. Presumably, in these conditions, the serum MB isoenzyme comes from damaged myocardial fibers. None of these conditions are likely to be confused with acute myocardial infarction.

Salient Features of the MB Isoenzyme of CPK

Presence in serum is highly specific for recent myocardial injury.

Appears in serum soon (two to six hours) after myocardial infarction.

Presence in serum in transient: may be gone by 36 hours after infarction.

Is not detectable in serum in congestive heart failure, pulmonary embolism, chest wall pain, angina pectoris, or after IM injections or surgery.

Some conditions other than myocardial infarction may have serum MB isoenzyme. These are hypothyroidism, polymyositis, muscular dystrophy, CO poisoning, malignant hyperthermia.

About 50% of patients admitted to coronary care units are found, subsequently, not to have had infarction. The ability to determine reliably and rapidly whether or not infarction has occurred may have significant economic as well as medical

*Department of Pathology, North Memorial Medical Center, Minneapolis, Minnesota.

Adapted from a Grand Rounds presentation to the Department of Laboratory Medicine and Pathology, University of Minnesota, January 24, 1975.

aspects. If CPK isoenzymes are determined routinely, infarction can be ruled in or out, in the great majority of cases, within 12 to 24 hours of admission. This may bring about better utilization of limited and expensive coronary surveillance facilities.

References

1. Mercer DW: Separation of tissue and serum creatine kinase isoenzymes by ion-exchange chromatography. Clin Chem 20:36, 1974.
2. Roberts R and Sobel B: Isoenzymes of creatine phosphokinase and diagnosis of myocardial infarction. Ann Intern Med 79:741, 1973 (Ed).
3. Wagner GS, Roe CR, Limbird LE et al.: The importance of identification of the myocardial-specific isoenzyme of creatine phosphokinase (MB form) in the diagnosis of acute myocardial infarction. Circulation 47:263, 1973.

Fanconi's Syndrome

In children this syndrome may include a wide variety of birth anomalies, congenital defects, and associated hematologic and renal metabolic disturbances. In the 18 reported adult cases marked biochemical manifestations were present, including osteomalacia, pseudofractures, hypophosphatemia, renal glycosuria, and aminoaciduria with hyperaminoacidemia. The syndrome was described by de Toni (1933), Debré (1934), and Fanconi (1931, 1936). There is a familial tendency, and the disorder is probably transmitted as a Mendelian recessive trait.

The hematologic changes, most evident in younger patients, consists of hypoplasia of the bone marrow, anemia, leukopenia, thrombocytopenia, and in a few instances leukemia and multiple myeloma. Ecchymoses and hemorrhage occur in mucous membranes, and hyperpigmentation of the skin may occur as a result of hemosiderosis. Blood chemical alterations consist of an increased renal excretion of amino acids with or without cystinosis, an increased renal phosphate clearance with hyperphosphaturia, normal glycemia with renal glycosuria, acidosis associated with hyperchloremia, high urinary ammonia, and high urinary titratable acidity. Storage of cystine in the tissues of the reticuloendothelial system occurs, especially in the liver, lymph nodes, spleen, bone marrow, and kidneys. In many respects the adult cases resemble Milkman's syndrome.

Little is known concerning the cause. The chronic organic acidosis is thought to result from an inborn error of protein metabolism. There is, presumably, an abnormal function of the proximal convoluted renal tubules, in which crystals have been found, with a failure to reabsorb glucose, phosphate, amino acids, bicarbonate, potassium, and uric acid. Progress of the condition in adults may be very slow. The prognosis may be unfavorable if renal function is decreased.

Therapy consists of symptomatic measures and correction of the electrolytic imbalance. Large doses of vitamin D and a high intake of calcium and phosphorus are indicated. An alkalinizing mixture of potassium chloride, sodium citrate, and citric acid is used to correct the systemic acidosis. Transfusions are often necessary for the severe anemia. Splenectomy was of value in only two of seven cases recorded in the literature.

Durham, Robert H.—Encyclopedia of Medical Syndromes
Hoeber Medical Division, Harper and Row, New York

Continuing Medical Education

April/May

Miller-Dwan Hospital and Medical Center

Duluth Clinic Conference, May 3, Dwan Auditorium, Miller-Dwan Hospital and Medical Center, Duluth, May 3, 1975. Contact: Mrs. Linda Patterson, Miller-Dwan Hospital at (218) 727-8762, Extension 279. Conference title: "Treatment of Rheumatoid Arthritis."

American Medical Association Regional Conference

July 26 and 27, Minneapolis. (Details later).

American Medical Electroencephalographic Association

April 12-16 at the Safari Hotel in Scottsdale. Meeting will deal with clinical electroencephalography. Contact: R. P. Jeub, M.D., 825 Nicollet on the Mall, Minneapolis 55402.

American Board of Family Practice

Two-day written certification examination on November 1-2, 1975. Will be held at five centers in the United States. Write: Nicholas J. Pisacano, M.D., University of Kentucky Medical Center, Annex #2, Room 229, Lexington, Ky. 40506. Must file a completed application with the Board Office by June 15, 1975.

University of Minnesota

Registration information: Office of Continuing Medical Education, University of Minnesota, Box 293, the Medical School, Minneapolis 55455, or by phone (612) 373-8089. Courses offered are:

Allergy—April 3-5

An annual course, provides a review of applied clinical knowledge and recent advances. Includes the well known Blumenthal Memorial Lecture.

Current Trends in Cancer Diagnosis—April 23-25

Recent advances in laboratory methods, as aids to diagnosis, effective treatment and management will be emphasized in this course.

Ophthalmology, May 5-6

The topic is Cataracts, including an up-to-date review of phakoemulsification technique and intraocular lenses.

Clinical Dermatology for Family Practitioners, May 15-17

A practical updating and review of clinical applications, enhanced by opportunity for participant discussion of problem cases.

Perinatology, May 16-17

Course content is designed to provide specific, practical guidance to physicians and nurses whose practice may include high-risk mothers and infants. This course will be held at Marshall, Minnesota.

Current Concepts in Radiation Therapy, May 28-30

The course will present comprehensive reviews in tumors of the central nervous system, breast cancer, Hodgkins Disease and the non-Hodgkins lymphomas.

Fundamentals of Clinical Hypnosis, May 30-June 1

Sponsored jointly by the Departments of Psychiatry and Family Practice, and the American Society of Clinical Hypnosis, this course offers both introductory and advanced sections.

Great Plains Organization

Meeting to be held at Ramada Inn, Bloomington, May 19 and 20. Theme for meeting will be care of perinatal patient in the community. Write: Ruth Redmond, R.N., Wisconsin Perinatal Center, 202 South Park St., Madison, Wisconsin 53715.

Metropolitan Medical Center

Neurology

Conferences, Fridays, 8:30 a.m., Center Building, Conference Room, 900 So. 8th St., Minneapolis. Contact: Mary J. Donner, Metropolitan Medical Center—338-7744.

Audio-Visual Network for Continuing Education

9:00 a.m. in Doctor's Lounge, second Tuesday of each month, 900 South 8th Street, Minneapolis. Contact: Margie Knutson, Metropolitan Medical Center, 338-7744.

Tumor Conference—Cancer

Every Monday except if a holiday. 12:00 noon, 900 South 8th Street, Lower Level Conference Room. Contact: Dr. Lyle J. Hay, MMC, 338-7744.

See other listings, pages 312, 319 and 352

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Group Excess Major Medical – $100,000 with $25,000 deductible

Group Life – up to $100,000 – premium credit dividends have averaged 29.33% since 1959 (Dividends cannot be guaranteed)

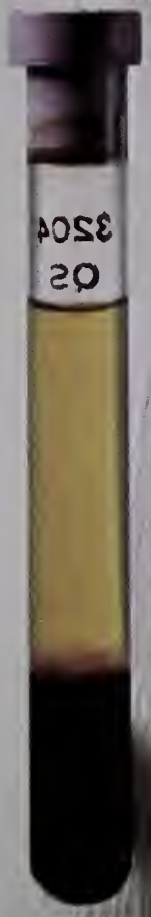


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See reverse side for full prescribing information

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Four strengths . . . 1, 2, 4, and 6 mg. . . . are available making the scored tablet regimen a flexible dosage system. And, for most patients, CHOLOXIN tablets offer once-a-day dosage.

AN IMPORTANT NOTE:
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CHOLOXIN® (sodium dextrothyroxine) Single-Tablet-A-Day Dosage Schedules

See prescribing information in package insert reproduced below.

	Starting Dosage	Increased Monthly by	Usual Maintenance	Maximal Recommended
Adult Hypercholesterolemic	1.0-2.0 mg.	1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac	0.5-1.0 mg.	1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as D-3,5,3′,5′-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

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Fracture Conference

Fractures of the Neck of the Talus

GEORGE R. MONKMAN, M.D.;* KENNETH A. JOHNSON, M.D.† and DOUGLAS M. DUNCAN, M.D.*

Three cases of fractures of the neck of the talus are presented; each illustrates the classification of these fractures popularized by Hawkins in 1970. Displaced fractures are much more likely to lead to complications, especially avascular necrosis, than are undisplaced fractures. Anatomic reduction and internal fixation, if necessary for stability, is the suggested primary treatment of these fractures.

Dr. George R. Monkman:

In 1970, Hawkins[1] reported a clinically useful classification for fractures of the neck of the talus in which he described three types: type 1, an undisplaced vertical fracture of the neck of the talus; type 2, a vertical neck fracture and dislocation or subluxation of the body of the talus from the subtalar joint, with the tibiotalar joint being in normal alignment; and type 3, a displaced vertical neck fracture, with the body of the talus being dislocated from both the tibiotalar and the subtalar joint. I shall present three cases, each illustrating one of the types.

*Resident in Orthopedics, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.
†Consultant, Department of Orthopedics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
Reprint address: Dr. G. R. Monkman, c/o Section of Publications, Mayo Clinic, 200 First Street SW, Rochester, MN 55901.
Fracture Conference, December 31, 1973.

Case 1

The first patient is a 25-year-old man who fell seven feet from a ladder. He landed on a piece of angle iron and suffered a varus dorsiflexion strain of his ankle. Roentgenograms were taken in the emergency room (Figure 1).

Dr. Kenneth A. Johnson:

Would you read the Xrays for us, Dr. Crow?



Fig. 1 (Case 1)—Lateral *(A)* and anteroposterior *(B)* views show undisplaced fracture of neck of talus (Hawkins' type 1).

Dr. Joe W. Crow:

There is a vertical fracture in the neck of the talus. The talus is undisplaced. I do not see any disruption of the subtalar joint or the ankle joint.

Dr. K. A. Johnson:

This is a type 1 fracture of the neck of the talus. How would you suggest that this fracture be treated?

Dr. Crow:

I think I would place the patient in a short leg cast.

Dr. Monkman:

This was done. The cast was a short leg non-walking one. This was in place for three months; and the patient was treated with protected weight-bearing for an additional three months, using crutches initially and then a cane. These are Xrays taken six months after injury (Figure 2).

Dr. K. A. Johnson:

Dr. Osland, do you see anything on these Xrays that might indicate the presence of avascular necrosis of the body of the talus?

Dr. George L. Osland:

There is considerable osteopenia involving the distal tibia, fibula, and talus. Is that significant?

Dr. Monkman:

Well, it could be. The subchondral bone atrophy seen in the dome of the talus on the anteroposterior view rules out the presence of avascular necrosis. For subchondral atrophy to occur, a good vascular circulation is necessary, and thus, its presence in effect eliminates the possibility of avascular necrosis of the body of the talus. This is the so-called "Hawkins" sign.

Case 2

The second patient is a 36-year-old waitress who was involved in a one-car automobile accident after she had fallen asleep at the wheel. She went off the road, injuring her right ankle. She was brought to the emergency room, where Xrays were taken (Figure 3).

Dr. K. A. Johnson:

Dr. Horswill, could you tell us what you see in these Xrays?

Dr. Robert N. Horswill:

There is a vertical fracture of the talus associated with a dislocation of the subtalar articulation. This would represent a type 2 fracture of the neck of the talus as described in the Hawkins classification.

Dr. Monkman:

The neurovascular status of the patient's foot was intact, and the injury was a closed one.

Dr. K. A. Johnson:

How would you treat this injury?

Dr. Horswill:

The subtalar dislocation needs to be reduced. Initially, I would attempt closed reduction in the emergency room, utilizing intravenously administered analgesics. If this was not successful, I would try closed reduction with the patient under general anesthesia. I doubt that open reduction would be necessary.

Dr. Monkman:

The patient was taken to the operating room,

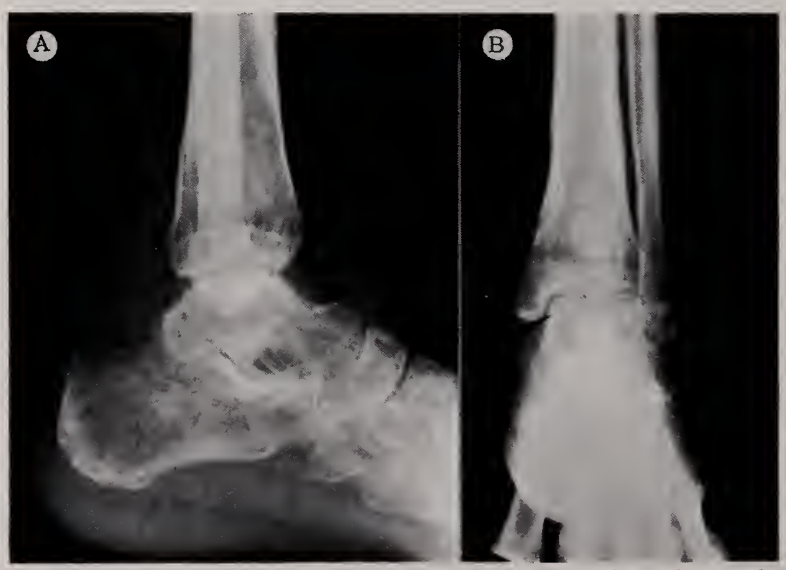


Fig. 2 (Case 1)—Lateral *(A)* and anteroposterior *(B)* views six months after undisplaced fracture of neck of talus. Subchondral atrophy in dome of talus *(arrow)* rules out possibility of avascular necrosis.



Fig. 3 (Case 2).—Lateral *(A)* and anteroposterior *(B)* views shows fracture of neck of talus, with body of talus displaced medially (Hawkins' type 2).

and closed reduction was achieved. The leg was placed in a long, bulky dressing with plaster reinforcement. After several days, a short leg nonweight-bearing cast was applied.

Dr. K. A. Johnson:

The dislocation was reduced (Figure 4). Dr. Braun, looking at a lateral view of the body of the talus, would you say that there is increased density on the Xray? (Such an increase is commonly considered x-ray evidence of avascular necrosis.)

Dr. Donald P. Braun:

Yes, although I know that avascular necrosis could not be roentgenographically evident only a few days after fracture.

Dr. K. A. Johnson:

If you are looking for an increased density of the body of the talus as a sign of avascular necrosis, you should not evaluate this on the lateral x-ray view. The anteroposterior view is the only talar view that gives an unobstructed evaluation of avascular necrosis. Follow-up Xrays at three months showed no increased density on an anteroposterior view of the talus, and there was some subchondral atrophy. Thus, these signs would make the development of avascular necrosis unlikely, and in fact, six months later, the patient had no adverse symptoms related to her ankle.

Case 3

Dr. Monkman:

The third patient is a 16-year-old boy who was a passenger in a car that apparently had a tire blowout, causing the car to go off the road over an embankment and into a river. The patient injured his left ankle and was brought to the emergency room with an obvious deformity of his left ankle and no palpable pulses in his foot.



Fig. 4 (Case 2)—Lateral view after reduction of type 2 fracture-dislocation. Overlying fibula gives more dense appearance to body of talus as if it might be avascular.

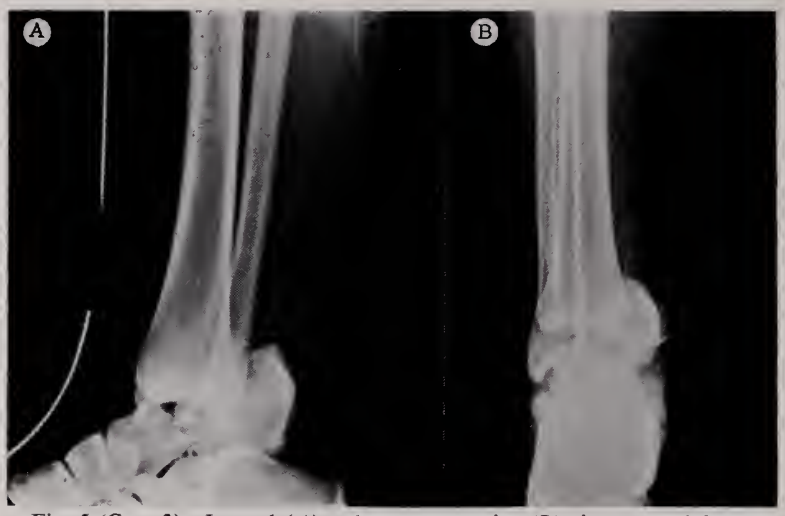


Fig. 5 (Case 3)—Lateral *(A)* and anteroposterior *(B)* views reveal fracture at neck of talus, with posterior medial displacement of body of talus out of ankle mortis (Hawkins' type 3). Medial malleolus is also fractured.

Xrays were taken of the ankle (Figure 5). Dr. Carlson, would you describe what you see on these Xrays and give us a plan of treatment?

Dr. Mark J. Carlson:

There appears to be a fracture of the neck of the talus, with a posterior displacement of the body of the talus from the tibia and calcaneus. This is a type 3 fracture of the neck of the talus. As to treatment, I would try to reduce the fracture in the emergency room using intravenously administered analgesics. If this was not successful, I would transfer the patient to the operating room as soon as possible for an attempt at closed reduction under general anesthesia, and open reduction if necessary. This is an emergency because the pedal pulses are absent.

Dr. Monkman:

Closed reduction was attempted in the emergency room, but this failed.

Dr. K. A. Johnson:

Dr. Morrey, do you see any additional fractures in the Xray (Figure 5)?

Dr. Bernard F. Morrey:

The medial malleolus appears to be fractured.

Dr. Monkman:

Correct. There is a fracture also of the medial malleolus. This patient was taken to the operating room, where open reduction was necessary and internal fixation was performed. Two Kirschner wires were placed across the talar fracture. A smaller Kirschner wire was placed in one of the small fragments of the medial malleolus, and a screw was placed in the larger fragment. Looking at the Xray taken two months after operation (Figure 6), Dr. Morrey, would you comment about any evidence of avascular necrosis on either of these views?

Dr. Morrey:

You can see on the anteroposterior view that the subchondral area of the talar dome is not atrophied; however, sclerosis is not present. Considering the injury, I think there is a good chance that avascular necrosis will occur.

Dr. Monkman:

Follow-up Xrays (Figure 7) taken two years later show that avascular necrosis of the body of the talus did develop.



Fig. 6 (Case 3)—Lateral *(A)* and anteroposterior *(B)* views two months after Hawkins' type 3 fracture-dislocation. No evidence of avascular necrosis.

Dr. K. A. Johnson:

Two years after his injury, the patient has avascular necrosis of the body of the talus, and the fractures appear to be healed. Dr. Sheehan, do you think that this patient should be allowed to walk with full body weight on that leg?

Dr. Joseph C. Sheehan:

How much pain did he have from his ankle?

Dr. Monkman:

The patient did not complain of any symptoms. The only clinical finding was that of moderately decreased motion of the tibiotalar and subtalar joints.

Dr. Sheehan:

After two years, I think that he should start full weight-bearing.

Dr. Monkman:

From the time of injury, he was nonweight-bearing for seven months and was on protected weight-bearing for an additional four months. Weight-bearing after several months makes little difference as to whether or not avascular necrosis of the body of the talus will develop.

Dr. K. A. Johnson:

We have seen examples of Hawkins' types 1, 2, and 3 fractures of the neck of the talus. Is there any further discussion?

Dr. Joseph M. Janes:

I have been surprised at the number of patients who have avascular necrosis of the body of the talus and yet who have very few symptoms. While on duty with the Royal Air Force during World War II, our group did primary tibial calcaneal fusions for injuries that were almost always associated with avascular necrosis of the talus, because such a fusion was considered to be the quickest way to get the patient back to active duty without pain. From my subsequent experiences, I think that many patients with avascular necrosis do not have too much trouble and that primary fusion probably was not the most effective treatment.

Dr. Douglas M. Duncan:

How would your group do the tibial calcaneal fusion, Dr. Janes?

Dr. Janes:

We would reduce the fracture and then place a bone graft on the lateral side of the ankle from tibia to calcaneus.

Dr. Duncan:

You did not do a Blair-type fusion,[2] in which an anterior sliding tibial graft is placed into the head and neck of the talus?

Dr. Janes:

No, we did not even know about Blair 30 years ago.



Fig. 7 (Case 3)—Lateral *(A)* and anteroposterior *(B)* views of type 3 fracture-dislocation two years after injury. Body of talus is sclerotic, indicative of avascular necrosis. Patient was experiencing no pain at this time.

Discussion

Dr. Monkman:

These fractures and fracture-dislocations are created by loading in the position of extreme dorsiflexion of the ankle, such as occurs in falling from a height or when a pilot crash lands and jams his foot into the floor boards of the rudder peddle, as has been described by Coltart.[3] The most common complication after fractures and fracture-dislocations of the talus is avascular necrosis of the body of the talus. Although percentages differ, all authors agree that the incidence of avascular necrosis increases with the severity of the injury. Hawkins[1] has the largest published series and reported no avascular necrosis associated with type 1 injuries. With the type 2 injuries, 42% of the patients later developed avascular necrosis, and with type 3, 91% developed avascular necrosis. The reason for these differences becomes apparent if one studies the blood supply of the talus.[4,5]

The talus receives its blood supply from all the major arteries that pass by it: the perforating peroneal, the dorsalis pedis, and the posterior tibial. These vessels combine to form a "sling" about the neck of the talus. From this "sling" arise the secondary arteries that penetrate through foramina and become intraosseous. Once inside the bone, the arteries course posteriorly into the body of the talus. This intraosseous course makes the body of the talus susceptible to interruption of its arterial blood supply. The more the displacement of the fracture, the greater the likelihood of the intraosseous blood supply being interrupted.

The treatment of these injuries remains controversial. The undisplaced fractures can be treated conservatively, with a minimal risk of complications such as avascular necrosis. Concerning fracture-dislocations, there exist proponents of nearly every form of treatment imaginable, from closed reduction and casting to primary subtalar, pantalar, or tibial calcaneal fusion. Examination of the literature reveals that better[6,7] results appear to be obtained by rapid, accurate reduction and subsequent immobilization than by other methods of treatment. Closed reduction usually should be attempted first, and if this fails, open reduction should be tried. If the fracture is not stable in a reduced position, an internal fixation device should be used. If infection does not supervene, this method appears to be the best primary treatment for closed fracture-dislocation. However, for the more severe injuries that are displaced, open, and contaminated, and in which treatment has been delayed, tibiotalar fusion, performed four to six weeks after possible infection has been controlled, may be the most effective.[8]

Considerable disagreement exists about the proper treatment of patients in whom avascular necrosis develops.[8,9] The avascular necrosis usually can be detected six to eight weeks after the injury. Hawkins[1] stated that evidence of subchondral atrophy in the dome of the talus on anteroposterior view rules out the presence of avascular necrosis. If, instead, this area appears to be sclerotic in relation to the surrounding bony structures, it can be assumed that the body of the talus is avascular. The presence of avascularity is a poor prognostic sign but is not incompatible with a reasonable functional result. Fracture healing can occur in the presence of avascular necrosis, but it is delayed. Secondary treatment, such as talectomy or arthrodesis, should be based on the symptoms and disability rather than on the roentgenographic finding of avascular necrosis alone. O'Brien et al.[10] believed that nonweight-bearing had no effect on the final outcome and did not restrict weight-bearing in their patients with avascular necrosis after the associated fractures were healed.

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Special Article

Perinatal Mortality in Minnesota

Guidelines to a Relevant Evaluation

RALPH A. FRANCIOSI, M.D.*

Since most neonates die in the first twelve hours after birth, an accent on perinatal medicine e.g. pregnancy, delivery and early postnatal infant care is needed. In the state of Minnesota a milieu exists for regional cooperation in handling perinatal problems.

STATISTICS ARE A superb mathematical tool, however their relevance is questioned in evaluating perinatal mortality. Unfortunately these statistics are used for national and international comparisons. Apparently the problems relate to an attempt to gather statistics in depth without proper medical input. Vital statistics are taken from certificates of birth, death, fetal death and reports of marriages and divorces. In assessing the problem of perinatal mortality, the birth, death and fetal death certificates are utilized. The collection and reliability of data on these certificates is not medically quality controlled and what appear to be firm statistics must be viewed in the light that even gross postmortem findings are scarcely used and indeed if used, are usually not definitive. The inaccuracies of certificates as a basis for health statistics have been noted.[1] The present report is an attempt to improve the relevance of vital statistics primarily in the area of neonatal mortality.

Materials and Methods

Minnesota has eight regions designated as health care regions by the State Health Department. A regional health care map was used to review neonatal deaths in Minnesota from July 1972 through December 1973. Live birth certificates linked with death certificates were reviewed for birth weight (in grams) and gestational age (calculated as the time from the onset of last menstrual period to date of delivery). The gestational age was recorded in completed weeks with four days or greater being counted as a completed gestational week. If either a birth weight or date of last menstrual period were missing, the figure given was considered a mean and used to determine risk as noted below. If both birth weight and date of last menstrual period were not recorded, the infant was not included in the study. The chart of Battaglia and Lubchenco[2] was used to ascertain the risk of dying. The risk of dying was divided into quartiles (quarters) by percent of total neonatal deaths, i.e. I. 0-25%; II. 26-50%; III. 51-75%; IV. 76-100%. Other data abstracted included length of life; performance of autopsy; hospital of birth; hospital of death; county of birth and county of death.

Results

Eight hundred and forty linked live birth and death certificates were reviewed. Table 1 lists the risk of dying in the eight regions in Minnesota. The largest percentages in each region are accounted for by quartiles I and IV.[2] The length of life (Table 2) was less than 12 hours in the majority of infants. The number of infants autopsied varied from 14-73% (Table 3). Except for Regions 7 and 8 most deaths occurred in the hospital and county of birth (Table 3). In Region 7, approximately one-fourth of infants dying were transferred from the hospital of birth out of the county. In Region 8, approximately 50% of in-

TABLE 1
Risk of Dying by Region (%)

Region	I 0-25	II 26-50	III 51-75	IV 76-100
1.	35.71	3.57	3.57	57.14
2.	38.57	17.14	5.71	38.57
3.	28.57	9.52	0.00	61.90
4.	23.21	14.29	3.57	58.93
5.	32.08	7.55	7.55	52.83
6.	40.82	8.16	20.41	30.61
7.	40.00	10.00	10.00	40.0
8.	41.43	10.20	10.00	38.70
Average	34.98	10.03	7.60	47.34

*Pathologist and Director of Laboratories, Minneapolis Children's Health Center, Minneapolis, Minnesota.

TABLE 2.
Length of Life by Region (%)

Regions	≤12 hrs.	13-48 hrs.	>48 hrs.	Unknown
1.	75.00	14.28	7.14	3.57
2.	57.14	22.86	17.14	2.86
3.	85.71	9.52	4.76	0.00
4.	80.36	12.50	7.14	0.00
5.	62.26	17.00	15.08	5.66
6.	59.18	18.37	20.41	2.04
7.	60.00	13.75	25.00	1.25
8.	38.16	20.41	41.43	0.00
Average	64.66	16.09	17.26	1.92

TABLE 3
Autopsy Data, Similar Hospital and Similar Counties (%)

Region	Autopsied	Similar Hospital	Similar County
1.	14.28	96.43	100
2.	57.14	95.71	100
3.	23.81	100	100
4.	21.43	95.08	96.72
5.	20.75	100	100
6.	36.73	93.88	93.88
7.	61.25	71.43	78.57
8.	73.06	48.78	76.94
Average	38.56	87.66	93.26

fants died in another hospital and 25% in a different county.

Discussion

The risk of dying forms a basis of many life insurance predictions. Applying this risk method to newborn infants seems logical and fortunately the data presented by Battaglia and Lubchenco[2] allows this approach. Since the predictions are based upon birth weight and gestational age, these data can be questioned as sources of error. Theoretically the weight data can be accurate, however the gestational age can vary according to the methods used for calculation. The date of the beginning of the last menstrual period plus one week, minus three months, classically is used to calculate the estimated date of confinement (E.D.C.). This method can be faulty on individual cases particularly where menstruation is irregular. Ideally confirmation of the E.D.C. can be made by physical examination of the infant or where indicated by amniocentesis. The latter procedure is not performed routinely, however it is gaining acceptance in selected instances e.g. high risk pregnancies and elective cesarean sections. In the present study, the interval between the date of last menstrual period and birth date was calculated as the gestational age. Although this method was known not to be ideal, the error seemed compensated by the 25% leeway in each quartile and the large number of infants reviewed. A more accurate estimation of gestational age may be recorded in the future with the aid of physical examination and amniocentesis.

Risk of Dying Inversely Proportional to Gestational Age

The risk of dying is inversely proportional to gestational age. This is indicated in Table 1 where 47% of neonatal deaths occurred in the IVth quartile. Understandably this number is high since essentially all infants in this group are less than 28 weeks gestation. The average risk of death in quartile I appears high at 35% but one must remember that this group is heterogeneous. Included are infants with underlying congenital malformations and those experiencing problems during labor and delivery. If one were to determine the exact cause of death in any quartile, other than birth and death certificate analysis is required. This detailed analysis which requires time and medical expertise can best be done by a perinatal study group.

Most Deaths in First 12 Hours

Approximately 65% of neonatal deaths occur in the first 12 hours of life (Table 2). This raises questions regarding perinatal care which accents transport of sick infants. More emphasis should be placed on pregnancy, labor, delivery and early postnatal care of the infant. This approach is essential to prevent high mortality and morbidity in the newborn. Table 3 indicates that a regional cooperative approach in Minnesota is feasible since most neonatal births and deaths occur in the same county and certainly in the same region.

The number of infants autopsied varies in regions and the reasons are apparently complex. At least an educational effort could be directed at determining what is a complete autopsy and what facilities are available to perform such autopsies. In addition, education should include familiarity with neonatal problems. A classical example of unfamiliarity with neonatal problems is the acceptance of the term "hyaline membrane disease" as a cause of death when this is more a sign than a disease entity.

Conclusions

Society is demanding that health care statistics be relevant to solving present and future medical

problems. Neonatal statistics are often inaccurate, cumbersome and of questionable relevance to defining problem areas. A method is presented that can indicate the risk of dying from birth weight and gestational age data. In order to evaluate cause of death in newborns a more detailed analysis is required. This detailed analysis cannot be obtained by reviewing linked death and birth certificates and will require a perinatal study group. In this way, the data could not only be quality controlled but kept confidential.

Acknowledgment

I would like to thank Mr. Frederick King, Chief of Vital Statistics, Minnesota Department of Health and his staff for their cooperation. In addition, Mrs. Louise Kundmueller was very helpful in accumulating statistical data.

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Dean S. Fleming, M.D.

Dr. Dean S. Fleming has retired as Director of the Division of Personal Health Services, Minnesota Department of Health after serving in that capacity from 1946 to 1974. In 1972 he was presented the Albert J. Chesley award by the Minnesota State Public Health Association, and from 1963 to 1965 served as President of the Conference on State and Territorial Epidemiologists.

Among his many accomplishments was the development of a rheumatic fever registry which is considered exemplary in the nation.

Dr. Barry S. Levy has been appointed the Acting Director of the Division and Acting State Epidemiologist.

Request for Physician's Art Work

For many years the Board of Editors of MINNESOTA MEDICINE has recognized and supported photographic and other artistic talents of the members of the Minnesota State Medical Association publishing cover pictures in color of their work. Our series of color covers have received much favorable comment and many journals have followed us in the use of color art in this manner.

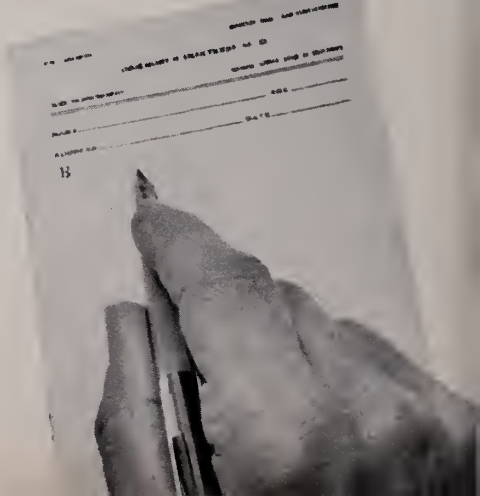
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Although in the past we have printed cover pictures depicting many distant parts of the world, photographs of life in Minnesota will be given preference. Pictures will be returned if identified with the name and address of the physician. Please submit your picture as prospective cover subjects to the Editor of MINNESOTA MEDICINE, 375 Jackson St., St. Paul, Minnesota 55101.

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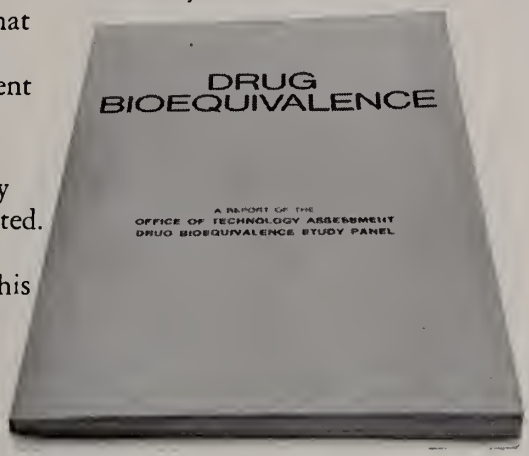
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Minnesota State Medical Association Nominees for State Offices

In cooperation with the House of Delegates, we are publishing short biographies of the nominees for Minnesota State Medical Association offices. In addition, any delegate may make nominations from the House of Delegates floor after the report of the Nominating Committee.

Each elected official will assume his position at the conclusion of the 1975 Annual Meeting. The current president-elect, Dr. G. R. Diessner, was elected in 1974 and will become president after the 1975 Annual Meeting concludes.

President-Elect

Chester A. Anderson, M.D.

Doctor Chester A. Anderson has been a family physician in Hector for 26 years. He received his B.A. degree at Macalester College and his M.D. degree at the University of Minnesota. Following his internship at Charles T. Miller Hospital, St. Paul, he served two years in the medical corps of the U.S. Army in Germany. Before moving to Hector, he practiced in Winsted for a short time.

Since 1972, Doctor Anderson has chaired the Association's Public Policy Committee. He also has been a member of the Family Practice Committee and the Committee on Medical School Relations. He serves as a delegate to the House from the Mid-Minnesota Medical Society.

He is active in the Minnesota Academy of Family Physicians and has held most offices of the organization. He was president in 1970. In 1974, he received the Merit Award from the Academy.

Doctor Anderson is a Diplomate, American Board of Family Physicians and a Charter Fellow, American Academy of Family Physicians.

Active in his local community, he has served on the board of the Chamber of Commerce. For the past 21 years, he has served on the Hector School Board and spent the past three years as its chairman. He is a member and leader of the Hector Methodist Church.

Doctor Anderson is married and has four daughters. He likes reading, swimming and water skiing.

Richard E. Anonsen, M.D.

Current Speaker of the House of Delegates, Doctor Richard E. Anonsen, practices at the Tyrol Clinic, Minneapolis. He is in family practice and is a Diplomate, American Board of Family Physicians.

Doctor Anonsen was born in Willmar and received his undergraduate education at the University of Minnesota. In 1954, he received his M.D. degree from the University, then interned at Hennepin County General Hospital.

During World War II, he served in the Pacific with the U.S. Navy and Marine Corps.

He is a member of the Hennepin County Medical Society, American Medical Association, Alpha Omega Alpha and Academy of Family Physicians. He is a past president of the Hennepin County Chapter of the Academy of Family Physicians; past president and chairman of the board of directors of the Hennepin County Medical Society and the Foundation for Health Care Evaluation. He is past chief of staff of Eitel Hospital.

With the Association, Doctor Anonsen has been speaker of the House for three years. Prior to becoming speaker, he served as a member of the Committee on Medical Service and its Subcommittee on Medical Care Standards and as vice speaker.

He is married and the father of four daughters. He likes water skiing, snow skiing and hunting.

First Vice-President

Robert A. Rovelstad, M.D.

Minnesota born Doctor Robert A. Rovelstad's education and career as a physician has taken him in and out of Minnesota.

He began his higher education after serving as a naval aviator, 1943-45. He was graduated from St. Olaf College, Northfield, 1949, and Northwestern University Medical School, Chicago, 1953. He interned at Minneapolis General Hospital and became a family practitioner in Fairmont. Two years later he returned to school to complete his surgical residency at Columbia-Presbyterian Medical Center, New York, 1960. He became a staff surgeon at Henry Ford Hospital, Detroit and in 1962 began his practice as a surgeon in Streator, Illinois.

FOR CORRECTION SEE p. 384

Since 1970, he has practiced in St. Cloud and for two years served as chief, Department of Surgery, St. Cloud Hospital. He is also Senior Aviation Medical Examiner there.

Doctor Rovelstad is a Fellow, American College of Surgeons; Fellow, Minnesota Surgical Society; Associate Fellow, American College of Chest Physicians; member, AMA, Stearns-Benton County Medical Society, St. Cloud Medical Society; and a Diplomate, American Board of Surgery and American Orthopedic Association. He is a member of the MSMA Cancer Committee.

Doctor Rovelstad is married and he and his wife, Ardis, a dietician, have three children. He is active in the St. John's Episcopal Church, St. Cloud. He lists his hobbies as music and aviation.

Horatio P. Van Cleve, Jr., M.D.

Doctor Horatio P. Van Cleve, Jr., Austin family physician, has a special interest in the education and training of physicians and currently chairs the Association Medical Education Committee, a position he has held since 1971. He has served as preceptor of the Department of Family Practice at the University of Minnesota Medical School and was an assistant professor in the Comprehensive Clinic program at the school.

In addition, he has chaired the MSMA Insurance Liaison Committee, 1960-68. Doctor Van Cleve was vice speaker of the House of Delegates, 1968-70. This year he serves on the Scientific Assembly Committee.

Doctor Van Cleve was born in Cranford, New Jersey, but moved with his family to Minneapolis as a youngster. He was graduated from the University of Minnesota, 1942, followed by graduation from the University Medical School, 1944. He interned at Minneapolis General Hospital and did post-graduate work at Swedish Hospital, Minneapolis, in general surgery. He practiced at Dodge Center for three years before joining the Austin Clinic in 1950 where he remains in practice today.

Doctor Van Cleve's subspecialty is dermatology and he is a member of the Minnesota Dermatologic Society and American Academy of Dermatology.

Second Vice President

John M. Burns, M.D.

Current chairman of the Local Arrangements Committee, Doctor John Burns, has been a member of the Ramsey County Medical Society for the past 13 years and of the Association for the past 15 years. Presently, he is engaged in group practice in internal medicine in St. Paul. His subspecialty is nephrology and he is a member of the MSMA Committee on Hemodialysis and Transplantation.

Doctor Burns attended St. Louis University, St. Louis, Missouri, obtaining his B.S. degree, 1954, and his M.D. degree, 1958. He interned at St. Louis City Hospital, St. Louis, and did postgraduate work at Minneapolis V.A. and Ancker Hospitals.

He became a fulltime staff member of the Department of Internal Medicine, Section of Renal Disease, 1964, and Director of the St. Paul Ramsey Hospital Renal Clinic, 1965, a position he held until 1974.

Doctor Burns is board certified in internal medicine and is assistant clinical professor, internal medicine, University of Minnesota.

Secretary

Robert L. Powers, M.D.

Rochester born Doctor Robert L. Powers received his M.D. degree in 1959 from the University of Minnesota. Following graduation, he interned at St. Joseph's Hospital, St. Paul, and since has been in family practice at the Lexington Larpenteur Medical Center, P.A., St. Paul. Now living in St. Paul, Doctor Powers and his wife, Ruth, have eight children. His family is interested in skiing and water sports.

Doctor Powers is a Ramsey County Medical Society delegate to the Minnesota State Medical Association and has served as secretary of the Association for the past two years. He is a member of the American Medical Association, the Minnesota Academy of Family

Physicians, the Civil Aviation Medical Association and a fellow, American Academy of Family Physicians.

Currently he is on staff at St. Joseph's Hospital, Children's Hospital and United Hospitals, St. Luke's Division, where he is also on the teaching staff. Doctor Powers is an Assistant Clinical Professor of Family Practice and Community Health at the University of Minnesota.

Vernon L. Sommerdorf, M.D.

Doctor Vernon L. Sommerdorf, family physician, has practiced on the east side of St. Paul for the past 22 years.

He has always maintained an interest in politics and in 1964 was elected to the Minnesota House of Representatives. For eight years, Doctor Sommerdorf successfully combined the rigors of legislative commitee meetings and house sessions with the usual family physician's chores. Then, in 1972, he chose not to run.

Doctor Sommerdorf has been politically active with the Association, too. He has served as a representative in the fifth district for the Public Policy Committee since 1970. He is also a member of the Medical Service Committee and Subcommittee on Allied Health Personnel.

He received his medical education at the University of Minnesota Medical School. He interned at Ancker Hospital, St. Paul.

Doctor Sommerdorf is married and has three daughters and one son.

Treasurer

James C. Mankey, M.D.

Minneapolis native Doctor James C. Mankey still serves the Mill City as internist. He attended the University of Minnesota Medical School, graduating with his M.D. degree in 1943. He interned at Milwaukee County General Hospital and began his residency which was interrupted by military service. In 1948 he completed his residency at Milwaukee County General Hospital.

Doctor Mankey is a member of the Hennepin County Medical Society, American Medical Association, Minnesota Society of Internal Medicine, and Minneapolis Society of Internal Medicine.

He is board certified in internal medicine and is a fellow in the American College of Physicians.

Matt K. Plasha, M.D.

Doctor Matt K. Plasha founded the Coon Rapids Clinic in 1953 and remains there in family practice. Born in Duluth in 1920, Doctor Plasha graduated from the University of Minnesota Medical School in 1945. He interned at Harper Hospital, Detroit, and served in the U.S. Army for two years. Before moving to Coon Rapids, he was in family practice in Glenwood for five years.

Doctar Plasha is a past president of the Minnesota Academy of Family Physicians and an alternate delegate to the American Academy of Family Physicians. For many years he has been a delegate to the Minnesota State Medical Association. He is a diplomate, American Board of Family Physicians and in 1967 he served as chief of staff at Mercy Hospital, Coon Rapids.

He and his wife, Dorothy, have seven children.

Speaker

Frederick E. Drill, M.D.

Doctor Frederick E. Drill, Minneapolis orthopedic surgeon, is chairman of the board, Minnesota Foundation for Health Care Evaluation. Earlier, he was president of the Foundation for two years.

He was graduated from Harvard University and the University of Minnesota Medical School and interned at Minneapolis General Hospital. He completed his general surgery residency in 1958 at Minneapolis General Hospital and his orthopedic surgery residency in

1961 at the Minneapolis V.A. Hospital. He is now clinical associate professor, orthopedic surgery, at the University of Minnesota.

Doctor Drill has been a delegate from the Hennepin County Medical Society to the MSMA House of Delegates for eight years. He is a member of the Medical Testimony Committee. He is also a member of the American Medical Association. In 1970, he was chief of staff at Methodist Hospital, Minneapolis.

Doctor Drill is married and has four children.

James W. Halvorson, M.D.

For many years, Doctor James W. Halvorson, Zumbrota, has been an active member in the Minnesota State Medical Association. Besides membership on the Committees on Mental Health and its Subcommittee on Alcoholism and Other Chemical Dependencies; Automotive Injuries; and Interns, Residents and Medical Students, he has been a legislative contact physician for the Public Policy Committee, MSMA vice president, 1971-72, and vice speaker, 1974-75. He is chairman of the Association sponsored Discussion Group Concerned with the Alcohol-Impaired Driver and Highway Safety.

A past president of Goodhue County Medical Society, he serves as one of its delegates to the MSMA House of Delegates. He is on the Board of Editors of MINNESOTA MEDICINE.

Doctor Halvorson is a former member of the Minnesota State Board of Health and of the regional advisory group to the Northlands Regional Medical Program.

Known for his work combating alcoholism and in programs relating to the drinking driver, Doctor Halvorson was given the AAA Service to Motoring Award in 1972. He is vice president of the Minnesota Council on Alcohol Problems and serves on the Advisory Committee to the Hennepin County Alcohol Safety Action Project.

Doctor Halvorson is a native of Brainerd. He received his medical training at the University of Missouri and University of Minnesota and interned at St. Mary's Hospital, Duluth. He has been in family practice in Zumbrota for nearly 20 years and is a Diplomate, American Board of Family Physicians and a Charter Fellow, American Academy of Family Physicians.

Vice-Speaker

Severin H. Koop, Jr., M.D.

St. Cloud otolaryngologist Doctor Severin H. Koop is currently president-elect of the Minnesota Academy of Ophthalmology and Otolaryngology. He is clinical assistant professor at the University of Minnesota Department of Otolaryngology.

Doctor Koop attended St. Thomas College for three years before entering the University of Minnesota Medical School where he received his M.D. degree in 1955. He interned at Ancker Hospital, St. Paul, and was in the U.S. Army medical corps for two years before entering general practice in St. Cloud, 1959-62. He completed his residency in 1966 and was board certified the same year.

He lists membership in the Stearns-Benton County Medical Society, American Medical Association and American Academy of Ophthalmology and Otolaryngology. Presently he is vice president of the Stearns-Benton Medical Society. In addition, he is on the Council of Otolaryngology of the American Academy of Ophthalmology and Otolaryngology.

Doctor Koop likes tennis, fishing, photography and skiing. He and his wife, Ruth, have six children.

Robert Hugh Monahan, M.D.

Doctor Robert Hugh Monahan is a member of the MSMA Committee on Ophthalmology which he served as chairman for approximately 10 years. In addition, he was a member of the Committees on Medical Education, Rehabilitation, and University Relations. For two years, he served as vice-speaker of the House of Delegates.

Doctor Monahan was born in International Falls. He received his B.S. degree, 1940, M.B. degree, 1942, and M.D. degree, 1943, from the University of Minnesota. He interned at Charles T. Miller Hospital, St. Paul, and completed his residency in ophthalmology in 1950

at the University of Minnesota. Doctor Monahan was a fellow in eye pathology at the Massachusetts Eye and Ear Infirmary and in Ophthalmology at Harvard Medical School. In 1951, he became a diplomate in the American Board of Ophthalmology.

He has held a number of teaching appointments and currently is clinical professor, Department of Ophthalmology, University of Minnesota.

He is a member of the American and Minnesota Academies of Ophthalmology and Otolaryngology; American and Minnesota Associations of Ophthalmology; Pan American Ophthalmological Society; Pan American Eye Pathology Society; Midwest Eye Pathology Society; National and Minnesota Societies for the Prevention of Blindness; Georgiana Theobold Society, and the American Institute of Parliamentarians.

He has held numerous administrative positions including director of medical education in ophthalmology, Ancker Hospital; chief of staff, St. Paul-Ramsey Hospital and Medical Center; president, Minnesota Medical Alumni Association; president, Joint Commission on Allied Health Personnel in Ophthalmology; president, Minnesota Association of Ophthalmology and president, Minnesota Academy of Ophthalmology and Otolaryngology. He is the immediate past president, Association of Ophthalmology.

Doctor Monahan is a prolific writer on ophthalmic subjects and has published in many journals. He also has presented numerous papers before professional groups of ophthalmology.

Annual Meeting

The Minnesota State Medical Association's Annual meeting is in St. Paul, May 21-23, 1975, at the St. Paul Hilton Hotel .

Minnesota State Medical Association Annual Meeting

COME

MEET

EDUCATE

An Invitation to Meet . . .

The best way to find reasons to meet at the Annual Meeting is to have a meeting. So, Doctor John Burns and I met. We hadn't finished our first cup of coffee before realizing there isn't one good reason to bring you to St. Paul for Annual Meeting. There are a hundred!

You can meet with your colleagues from around the state while you take part in a variety of interesting and challenging scientific programs. And, while you're boning up on the latest medical techniques, procedures and innovations, you'll be on your way to meeting the new CME requirements for MSMA membership. Annual Meeting lets you earn up to 14 credits and enjoy a mini-vacation at the same time. Can you think of a better way to get an education?

The educational action takes place at the St. Paul Hilton Hotel in seminars and general sessions; seminars are limited to 100 or less attendance, general sessions open to 350. In addition, the many facets of health care and related industries will be represented by scores of technical and scientific exhibits. Most of us enjoy meeting with exhibitors and since the exhibits are located right in the Hilton, it will be convenient to do so.

A breakfast meeting with your specialty group or the MSMA committee on which you serve may be on your schedule. Maybe you've planned to meet with friends you see only at the Meeting for that once-a-year visit over coffee and Danish. Or, skip going out and have room service deliver breakfast. Business or pleasure, fancy or Continental, or delivered to your door, even breakfast is a special pleasure during Annual Meeting.

You won't want to miss the opportunity to meet this year's many distinguished guests and speakers. Doctor Malcom Todd, President of the American Medical Association, has accepted our invitation to come to the Meeting. Following a press conference, Doctor Todd will be joining members at the President's Reception and Annual Banquet on Thursday night and speaking to the MSMA House of Delegates on Friday. Among the Meeting's guests are Doctor William Nolen, surgeon and well known author. Doctor Nolen's practice in general surgery is in Litchfield, Minnesota but his avocation of writing has put him on the best-sellers' list, earned him guest spots on national TV and taken him around the world. He will speak on the Doctor/Patient Communication Gap at our Thursday luncheon. Doctor Elisabeth Kubler-Ross, noted physician/psychiatrist and pioneer thanatologist, is our Friday luncheon speaker. Most of us are familar with Doctor Ross through her books dealing with death and dying. Doctor William Fifer of the Health Policy Division of Interstudy, Vernon E. Weckworth, Ph.D., University of Minnesota, and Doctor William Roy, former Kansas congressman, will be taking part in the panel discussion of a most timely and important subject: The Physician and the Government. The 1975 program boasts an impressive array of participants and lecturers. Doctor Burns summed up the guest roster more succinctly: "It's Dynamite!" And, he's right.

John reminded me that golf and tennis champs among the membership will be meeting for some fierce, but friendly, competition at the White Bear Yacht Club Golf Course and the Lilydale Tennis Club. We remind you to bring your clubs or racquet if you want a shot at trophies awarded

the best players. To get into the competition, just register for your choice. Everything else is arranged for you. And, that includes a chauffeured ride to the club and escort back to your hotel when the games are over.

Athletes who prefer "working out" with knife and fork will find that St. Paul offers countless exercises in culinary enjoyment. Right in the Hilton you can sample Polynesian cuisine in the atmosphere of a South Seas island at Don the Beachcomber or enjoy leisurely and intimate dining in the elegant 1880's decor of The Parlour. You'll enjoy breakfast, brunch or lunch Scandinavian style in the Three Crowns Restaurant or Coffee Shop. Or, help yourself to a quick sandwich in the "Trapper's", a small room with the rustic feeling of the great Northwoods. And to top off this enticing assemblage, The Top of the Hilton! The "Top" is a most extraordinary departure in dining accommodations. It features an ever changing panoramic view of St. Paul made possible by the revolving carousel on which dinner guests are seated. A gourmet menu, elegant surroundings and beautiful view invite you to make your way to the "Top".

The half dozen Hilton restaurants are only a small sampling of the fine dining available in St. Paul. It is a city abundant with superb eating spots. Many offer foreign atmosphere and menu, others provide excellent entertainment. All serve a generous portion of St. Paul hospitality with their bill of fare.

Epicurean and entertaining night spots give way to a daytime kind of excitement in St. Paul. When the morning sun sparkles on the Mississippi and "downtowners" begin to fill the sidewalks, the city comes alive with its very own brand of cosmopolitan adventure. Rain or shine, shoppers can travel from boutique to department store, restaurant to art gallery, craft shop to ice cream parlor without going outside. The St. Paul skyway system links most downtown buildings with a climate controlled corridor in the air. This second floor thoroughfare allows carefree shopping in hundreds of shops and businesses in the downtown area. For the more adventuresome take a bus or cab to any of the suburban shopping centers and discover enticements akin to an old world bazaar where you may wander leisurely from shop to shop searching out your own special bargain. No haggling allowed, but, you may pause for that cup of tea, or an eggroll, or bagels or . . .

Beginning Wednesday afternoon you're invited to attend the open hearings of the reference committees. This is your opportunity as a member to contribute to the policy-making decisions of the Association. Did you know that you can speak to all of the issues being considered? Are you aware of how your governing body operates? Come and find out on May 21 when the reports and resolutions from county societies and association committees are reviewed and discussed. Since the issues facing today's physician have made national headlines, public attention will be focused on the critical decisions made by the "House." This year's session will be a dramatic episode in Minnesota medical history. Plan to be in St. Paul when the MSMA House of Delegates meets issues with answers.

Thursday evening. And, the Annual Banquet spotlights Fifty Club members. You'll want to be there when our members of the Club receive special honors for their fifty year dedication to medicine. John did some quick pen and napkin figuring to discover that the Fifty Club represents more than 2,000 years of medical experience! Tribute to the Fifty Club is only the beginning of the evening's festivities. Special awards for Distinguished Service, the President's Award and the Certificate of Merit will be given to outstanding MSMA physicians. Following award presentations, the famous Jules Herman Orchestra will provide entertainment for an evening of dancing and socializing. Music and dancing, the excitement of awards and the pleasure of meeting with guests and members will stir warm thoughts and memories long after the last waltz.

The Woman's Auxiliary has planned a collection of social and business activities for its members, too. The high point of the Auxiliary's two-day schedule is a tea at the Governor's residence on historic Summit Ave. Hosted by Governor and Mrs. Anderson, it promises to be a most interesting afternoon.

When the scientific session has ended on Friday, conviviality in the form of a Bavarian festival will begin. We're calling it a "Bavarian Beer Seminar" and hope that everyone who attends will learn something about German bands, beer and bratwurst. You won't earn credits for this "Seminar", but we know you'll leave with an authentic German beer stein and, we hope, some good memories of our first beer and brat fest.

Because Annual Meeting offers such a unique opportunity for education and great times, John suggested that perhaps we should have them more often. But, as I pointed out, "When it takes twelve months to plan an Association meeting like ours, it can only happen once a year!"

We've just scratched the surface for reasons why you should meet at the Annual Meeting. Join us in May to discover your own. Until then, Aufwiederschen!

John M. Burns, M.D.
Chairman
Local Arrangements

R. D. Semsch, M.D.
Chairman
Scientific Assembly

A Note about This Year's Scientific Program

When you receive your registration materials, you will find that the program format this year is somewhat different than in previous years. There will be several sessions conducted simultaneously, allowing you to choose the session you wish to attend during each time slot.

The Seminars will allow only limited attendance, so they require preregistration. If you wish to attend any of the seminars, you must indicate your choice on your registration forms when you send them in to the MSMA office. The seminars will be filled on a first come, first served basis, so early registration is advised. Admission to the seminars will be by ticket only. If the seminar of your choice is filled, the next choice available during that time period will be confirmed by letter.

The General Sessions will not be limited in attendance. This means that if you pay your registration fee and do not choose to attend any of the seminars, you will be admitted to the general sessions without a ticket. This also allows you the option of attending the general session if the seminar of your choice is unavailable.

An outline of the scientific program appears here to familiarize you with the format. We urge you to register early in order to be assured admission to the session of your choice.

Scientific Program

14 Hours, Accredited by AMA and AAFP
Exhibits Daily 8:30-5:00
Come Meet Educate

Thursday, May 22

8:30 a.m.-Noon:	"What's New In Dermatology?"—Seminar—Pioneer Suite
8:30 a.m.-Noon:	Part I—Diagnosis & Management Of An Acutely Painful Joint Part II—Prognosis & Management Of Various, Specific Orthopaedic Problems—Seminar—Senate Suite
8:30 a.m.-Noon:	Respiratory Problems—Seminar—Indian Suite
8:30 a.m.-Noon:	Surgical Infections—General Session—Minnesota West Ballroom
12:15 p.m.:	Luncheon—"Doctor-Patient Communication Gap"—William A. Nolen, M.D.—Minnesota East Ballroom
1:30-5:00 p.m.:	Continuing Education In Ophthalmology—Seminar—Pioneer Suite
1:30-5:00 p.m.:	The Physician And The Government—Seminar—Senate Suite
1:30-5:00 p.m.:	Infectious Disease—Seminar—Indian Suite
1:30-5:00 p.m.:	Immunology & Allergy—General Session—Minnesota West Ballroom

Friday, May 23

8:30-10 a.m.:	Treatment Of Rheumatoid Arthritis—The Old And The New—General Session—Minnesota West Ballroom
8:30 a.m.-Noon:	Symposium: Inflammatory Bowel Disease—Indian Suite
8:30 a.m.-Noon:	Colon And Rectum Cancer: Early Diagnosis, Prevention And Modern Day Treatment—Seminar—Senate Suite
8:30 a.m.-5 p.m.:	Human Sexuality In Clinical Practice—Seminar—Pioneer Suite
10:30 a.m.-Noon:	Chronic Pain: Genesis And Early Management—General Session—Minnesota West Ballroom
12:15 p.m.:	Luncheon—"Death And Dying"—Elisabeth Kubler-Ross, M.D.—Minnesota East Ballroom
1:30-3:00 p.m.:	Death And Dying—General Session—Minnesota West Ballroom

Business Sessions

Wednesday, May 21

10:00 a.m.:	New Delegates Orientation—St. Paul Hilton
Noon:	Credentials Committee—Hotel St. Paul
1:00 p.m.:	House Of Delegates, First Session—Ballroom, Hotel St. Paul
4:00-5:30 p.m.:	Reference Committee Meetings—St. Paul Hilton
7:00 p.m.:	Reconvene

Thursday, May 22

7:15 a.m.:	Committee Breakfasts—St. Paul Hilton
9:00 a.m.:	Reference Committees (if necessary)—St. Paul Hilton

Friday, May 23

7:15 a.m.:	Committee Breakfasts—St. Paul Hilton
1:00 p.m.:	House Of Delegates, Second Session—Ballroom, Hotel St. Paul

Specialty Society Meetings

Wednesday, May 21

6:00 p.m.:	Twin City Thoracic and Cardiovascular Surgical Society Quarterly Meeting—Town and Country Club, St. Paul

Thursday, May 22

12:15 p.m.:	Emergency Room Physicians Meeting—St. Paul Hilton
12:30 p.m.:	Minnesota Chapter, American College of Surgeons Annual Luncheon & Business Meeting—St. Paul Athletic Club
2:30-4:00 p.m.:	Woman's Auxiliary—President's Tea, Governor's Residence
6:30 p.m.:	Minnesota Allergy Society Inaugural Meeting—St. Paul Athletic Club

Friday, May 23

9:00 a.m.:	Woman's Auxiliary Annual Meeting & Luncheon—Minnesota Club

Saturday, May 24

8:00 a.m.:	Minnesota Society of Internal Medicine Semi-Annual Meeting—Minneapolis Veterans Administration Hospital
9:00 a.m.-4:00 p.m.:	Minnesota Physiatric Society—St. Joseph's Hospital, St. Paul

Classified Advertisements

Classified advertising rates are thirty (30) cents a word; minimum monthly charge $7.50; key number, $1.00 additional.

Replies to advertisements with key numbers should be mailed in care of Minnesota Medicine, 375 Jackson, St. Paul, Minn. 55101.

18 MAN MULTISPECIALTY clinic in scenic Coulee region of Western Wisconsin seeks general pediatrician preferably with subspecialty training in allergy. Contact: William A. Blank, M.D., La Crosse Clinic Ltd., 212 South 11th Street, La Crosse, Wisconsin 54601.

STAFF PHYSICIAN—Mankato State College is seeking a staff physician capable of general medicine and committed to working with young adults. Located in south central Minnesota the College has an on-campus enrollment of 9,500 students, and is situated in a metropolitan area of 50,000. Attractive five day work week, vacation when school not in session, position available July 1, 1975. Contact: Karen Delesha, Director, Student Health Service, Mankato State College, Mankato, Minn. 56001. Phone (507) 389-2726.

FAMILY PRACTICE opportunity with multi-specialty clinic. Separate departmental facilities in base community: satellite office in nearby rural community. Unique blending of primary and referral care in same group. Participate in this new approach to rural medicine. Generous starting salary first year incentive thereafter, liberal time off allowance and fringe benefits. Contact D. R. Molesworth, Administrator, Mankato Clinic Ltd., Mankato, Minn. 56001. Call collect 507-387-1811.

RIVERS EDGE MEDICAL CLINIC—Farmington, Mn. needs two additional General Practitioners to practice in a nearly new Clinic, Hospital and Nursing Home. Fast growing area just 45 minutes from St. Paul-Minneapolis. Metropolitan advantage with Community living. Contact M. H. Hunter, M.D. (612) 463-7181.

DOCTORS . . . RURAL MINNESOTA/WISCONSIN NEEDS YOU. (All Specialties)—A professional and time-saving approach to practice relocation. Enjoy the best of either world. Over 50 choice opportunities to choose from at no cost to you. For discrete and confidential assistance in helping you find the proper "niche" for you and your family. Call (612) 436-5161 collect. Midwest Medical, Inc., Lakeland, Minnesota 55043.

PHYSICIAN AVAILABLE for locum tenens for four weeks from middle of July. Has Minnesota license. Prefer Northern Minnesota. Write: MINNESOTA MEDICINE-508, 375 Jackson St., St. Paul 55101.

GROUP OR FAMILY PRACTICE—Over the past 3½ years the Fairmont Medical Clinic has added three new physicians to its staff. At the present time we are actively pursuing one additional man in general or family practice for the summer or fall, 1975. New clinic adjacent to a new 114-bed hospital in a rapidly growing community. Starting salary open, early partnership opportunity. Contact D. E. Grandgenett, Fairmont Medical Clinic. (507) 238-4263.

ST. CLOUD—Psychiatrists and other Physicians needed in VA Hospital. Excellent and cooperative social work, nursing, and psychology staffs. Fully staffed and newly equipped TV studio and hospital-wide CCTV network available for creative ideas to therapy, education and research. Training programs in Mental Health Associate, social work, psychology, nursing, occupational therapy. One hour to Minneapolis. Enjoy clean air and nearby camping, fishing, hunting, canoeing, downhill and cross-country skiing, snowmobiling and golf. Three local colleges with many cultural and educational advantages. License in any state accepted. Financial assistance in moving. Liberal vacation, sick, and health benefits. Excellent retirement plan. Salary dependent on professional qualifications. Nondiscrimination in employment. Write or phone collect: Chief of Staff, 612-252-1670.

PEDIATRIC NURSE PRACTITIONER AVAILABLE—Washington University graduate. Practicum experience with five Pediatrician group in St. Paul. Will relocate. Resume available. Contact: Darrell Rask, 1062 W. Iowa, St. Paul, Minn. 55117. (612) 489-2776.

OFFICE SPACE—Share large, well decorated suite in Minneapolis Medical Arts Bldg. 2 or 3 rooms plus shared reception room. Secretarial, bookkeeping, lab and chest x-ray services available on cooperative basis if desired. 333-1531.

Classified Advertisements

FOR RENT—Since I have joined the Air Force, my fully equipped modern office is for rent. 1600 square feet, four examining rooms, offices laboratory, waiting rooms. First floor, air-conditioned, ample parking. Monthly rental, $500. Write C. W. Anderson, M.D., 2117 S. Minnesota, Sioux Falls, S.D. 57105.

WANTED—G. P. to join well-established two-man family practice. Modern clinic building, new 38-bed hospital with 47-bed convalescent unit. Swimming pool, tennis courts, golfing, and fishing nearby. Contact: L. A. Knutson, M.D., Spring Grove, Minnesota 55974.

FOR SALE—ST. PAUL, MINNESOTA—Air-conditioned one-story brick building, 25 x 90 ft. Built 1946. Equipped for doctor, x-ray machines. Full basement, lot 75 x 125 ft.—John Johnson Realty, 605 Wells, St. Paul, Minn. 612-774-6004.

FAMILY PRACTITIONERS WANTED—Openings for five (5) Family Physicians in rapidly expanding, strictly family practice group ideally situated in Dakota County. The fastest growing county in Minnesota and the United States, serving the Twin Cities south suburban communities of Apple Valley, Burnsville, Eagen, Lakeville, Rosemount and Farmington, with a combined population of 75,000 to 150,000 residents. Salary guaranteed plus liberal incentive system (production bonus) first year, opportunity for full partnership second year if mutually agreeable. Twenty-four (24) hour work week (4 six hour days), call one day per week and every 10th weekend. This is a private fee for service office practice located in a brand new 14,000 sq. ft. facility (opened August 1974). You will have an opportunity for extra income by providing coverage in the 24 Hour Emergency Room located in the same facility. You can expect a first year income in excess of $40,000. You will be involved with a dynamic group of young family physicians (oldest is 38) who are setting precedents for innovations in providing complete, comprehensive, and accessible ambulatory care to the 75,000 to 150,000 residential population we exclusively serve. All five positions will be filled by the summer of 1975. If interested, contact Ralph Tharp, M.D., E. John English, M.D., Peter C. Frederixon, M.D., or Tom J. Pederson, Administrator, Family Physician Associates, 14655 Galaxie Ave., Apple Valley, Minnesota 55124. Telephone 612/432-6161.

MEDICAL BUILDING AND GENERAL PRACTICE—Medical building with 9-room medical suite and 6-room dental suite located in Northeast Minneapolis for sale. Dental suite is leased. At present the medical facilities are operated by the doctor, an assistant MD and a nursing staff. This is an opportunity for a younger physician or one who would prefer to change or improve his present situation as the doctor is interested in working toward retirement. All information confidential. Contact Fred Nelson, Brokers' Exchange, Inc., 4501 Minnetonka Blvd., Minneapolis, Minnesota 55416. Telephone 612-925-2477.

INTERNIST, ORTHOPEDIC SURGEON, OUTPATIENT PHYSICIAN, NURSE ANESTHETIST—Immediate staff vacancies available at the Iron Mountain VA Hospital, located in Michigan's Scenic Upper Peninsula. The community of 18,000 people offers excellent recreational and sports activities in an uncrowded, family environment. The hospital operates 234-GM&S beds and 40 nursing home care beds and is very well equipped. Current licensure in any state is acceptable; malpractice protection is provided under federal law. Contact: A. M. Holman, M.D., Chief of Staff, VA Hospital, Iron Mountain, MI 49801, phone 906-774-3300, Ext. 227. Nondiscrimination in employment.

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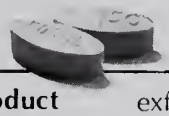
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Indications: Chronic urinary tract infections (primarily pyelonephritis, pyelitis and cystitis) due to susceptible organisms (usually *E. coli, Klebsiella-Enterobacter, Proteus mirabilis,* and, less frequently, indole-positive proteus species).

Note: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in chronic and recurrent urinary tract infections.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia in elderly patients on diuretics, primarily thiazides. Sore throat, fever, pallor or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. Data are insufficient to recommend use in infants and children under 12.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, allergy or bronchial asthma; and in those with glucose-6-phosphate dehydrogenase deficiency, where hemolysis may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

Dosage: Not recommended for children under 12.

Usual adult dosage: Two tablets b.i.d. for 10 to 14 days. For patients with renal impairment:

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Before prescribing, please consult complete product information, a summary of which appears on preceding page.

STATE MEDICAL ASSOCIATION

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MAY 1975

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Don L. Carlon, M.D.

Both often



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequ c and/or severity of grand mal seizures a require increased dosage of standard it convulsant medication; abrupt withdr a may be associated with temporary in- crease in frequency and/or severity o seizures. Advise against simultaneous i gestion of alcohol and other CNS depr- sants. Withdrawal symptoms (similar those with barbiturates and alcohol) h e occurred following abrupt discontinu c (convulsions, tremor, abdominal and u cle cramps, vomiting and sweating). I e addiction-prone individuals under car

respond to one

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with associated
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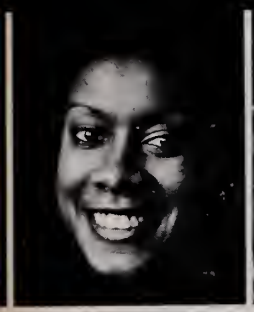
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President's Letter

Going Fishing

In my initial President's Letter, I wrote of the personal and professional challenges I expected to confront. It has been a year of challenges: long hours and disrupted schedules, steamed dinners at routine committee meetings and the tensions of crisis sessions, stacks of reading material and the monthly struggle to produce these letters.

In my response to these challenges I have tried to provide perspective on both the shortcomings and the problems of the medical profession. We all recognize that there are areas in which we as individuals can alter and improve. The impact of our organizational efforts on the legislature, the press, and the general public remains uncertain. Certainly continuing involvement and unremitting interest by all physicians is necessary to solve the problems which threaten the quality of health care for the people.

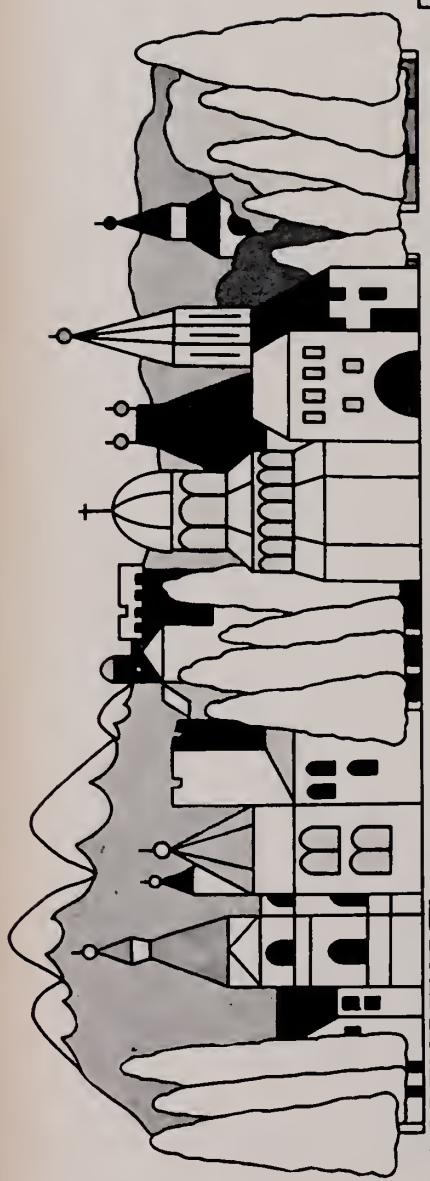
But if there have been challenges during this year, there have been also great rewards. I have not acted alone; the challenges have been shared. The staff of the Minnesota State Medical Association has been capable, diligent, interested, and tolerant. The encouragement of the Minnesota Medicine staff has made the writing of the President's Letter a not impossible task. My associates have accepted with good humor the many meetings and duties that frequently caused juggling of work assignments. My family and especially my wife, Blanche, have graciously accepted presidential demands that often interfered with more appealing activities.

Most of all, my duties have been lightened by the wholehearted, imaginative, and sincere responses of physicians throughout the state. Your interest has made the challenge of my year as President of the Minnesota State Medical Association memorable and rewarding. By your comments and criticisms I knew that my efforts were being understood and appreciated, if not always admired. There may indeed be some deficiencies in our organization, but they do not lie in the concern and commitment of the individual physician.

Bernard Hall M.D.

President
Minnesota State Medical Association





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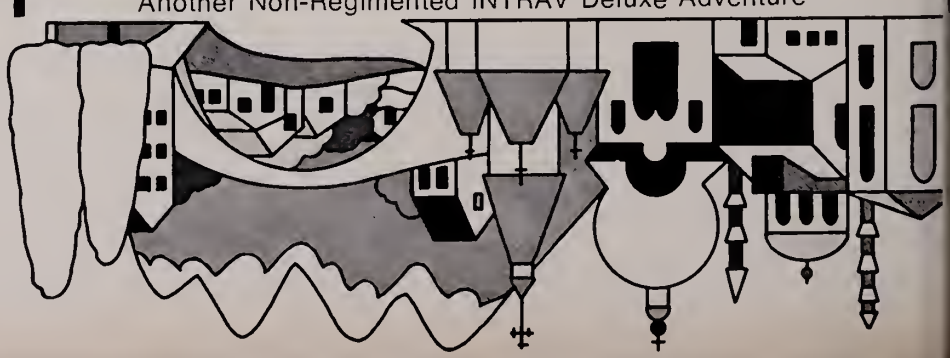
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the first of may

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the sun glows
the earth greens
flowers bloom
breezes blow
birds sing
and bugs stir
speaking for
the cockroaches
i say hooray
for the first of may
no more grubbing
for inside scraps
no more scrounging
in cold cellars
no more freezing
on frigid floors
no more groping
through early dusk
no sirree
from here on
i am going
to do my bugging
outside
i will
run free
think free
and breathe free
i will
let my spirit
float and set
my mind adrift
and when the urge
underwhelms me
i will
flip on my back
and let the sun
recharge my
batteries

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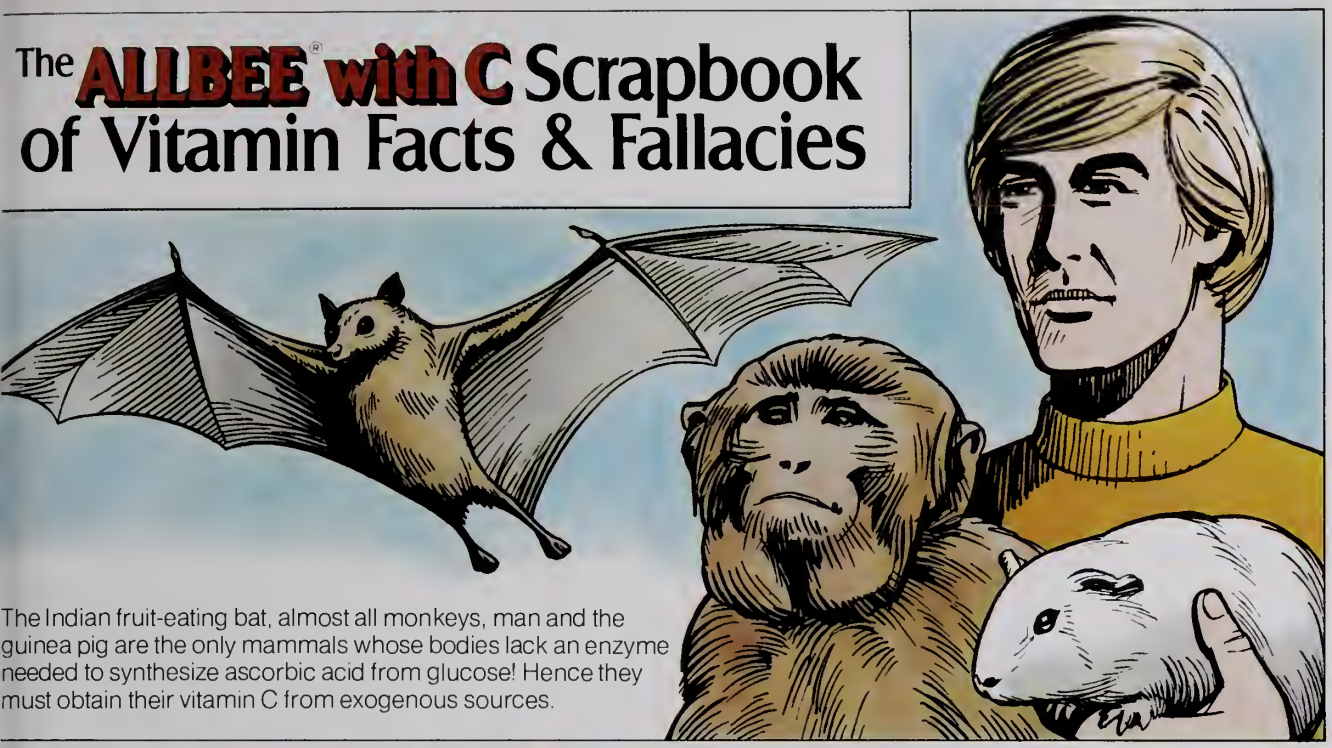
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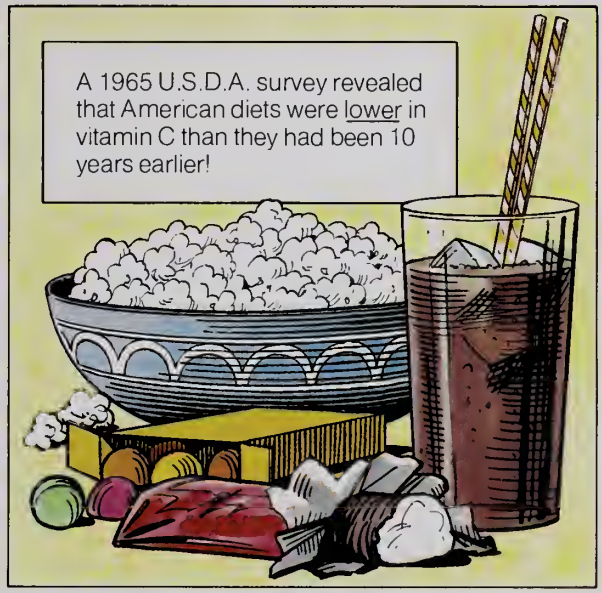


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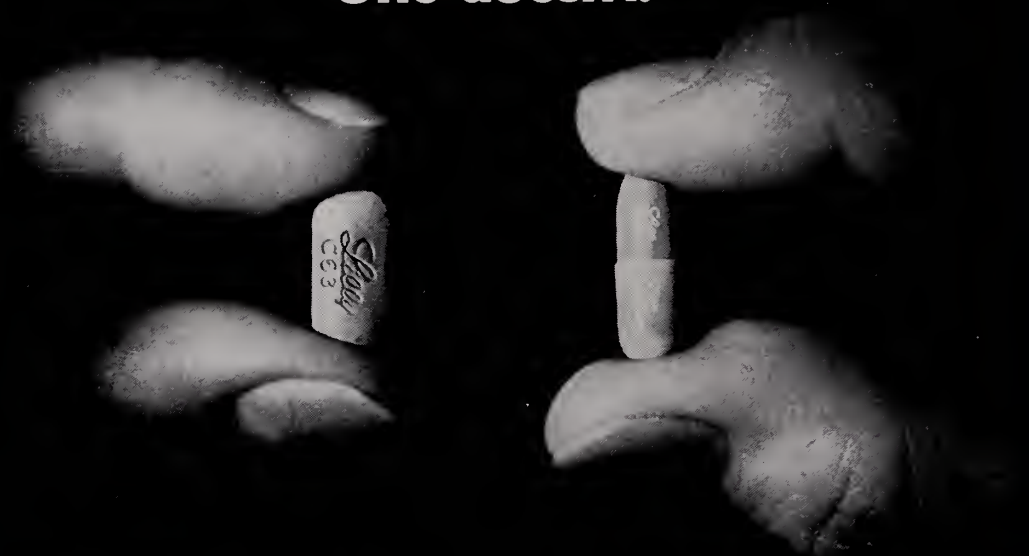
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Staphylococcal Empyema in Childhood

MELVIN P. BUBRICK, M.D.* and HOVALD K. HELSETH, M.D.*

The management of children with staphylococcal pneumonia and empyema is discussed. With the advent of effective antistaphylococcal antibiotics, treatment has been directed toward control of the primary disease process in the lung, and surgical drainage procedures are required far less frequently than in the past.



Fig. 1—Case 1. Chest roentgenogram 24 hours after admission showing right pleural effusion.

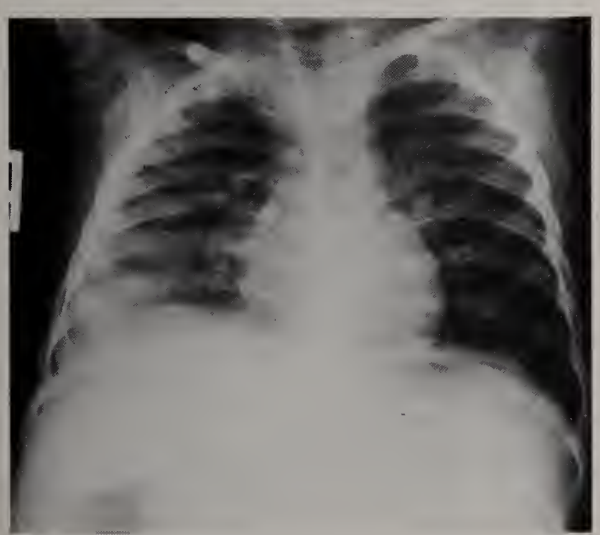


Fig. 2—Case 1. Early clearing of effusion after two weeks.

In recent years there has been a relative increase in the incidence of staphylococcal pneumonia and empyema in children despite an overall decrease in the incidence of empyema.[1,3,4,6] Because staphylococcal pneumonia and empyema in children once were associated with high mortality rates, aggressive surgical approaches were advocated by many authors.[1,4] Immediate chest tube drainage of the pleural space, followed when necessary by conversion to open drainage and, occasionally, decortication in 2-3 weeks were advised.[4] Some surgeons preferred multiple thoracenteses followed by closed thoracostomy drainage only if the initial fluid was thick.[1]

As a result of antibiotics, treatment of children with staphylococcal pneumonia and empyema has changed gradually. Two cases are presented to illustrate some current principles in the management of these problems.

Case Reports

Case 1

A 12-month-old Indian male was hospitalized after a three day illness consisting of coryza, cough, irritability and fever. The significant findings on physical examination were temperature 106°F, left otitis media, diffuse rhonchi in both lungs with rales in the right midlung field and expiratory wheezes at the left base. On admission the chest roentgenogram was normal and the leukocyte count was 12,400 (72% neutrophils). Diagnoses of otitis media and possibly early pneumonia were made and Ampicillin (500 mg/day orally) begun. By the following evening, the child was still febrile (temperature 104°F) and had developed significant respiratory distress with grunting respirations. Rales were noted over the right middle and lower lobes. The leukocyte count had increased to 22,200 with 81% neutrophils.

*Department of Surgery, Hennepin County General Hospital, Minneapolis, Minnesota 55415.

Chest Xray revealed a right pleural effusion (Figure 1). Thoracentesis returned 20 cc of clear yellow fluid which was negative on smear but bacteriologic cultures revealed coagulase positive staphylococcus. The child was given parenteral methicillin (2.0 gm/day) and penicillin G (1.6 million units/day).

During the next five days the child remained febrile with an increased leukocyte count, but the signs of respiratory distress diminished gradually. The chest roentgenogram remained unchanged. At this time the surgical service was consulted and a second thoracentesis was done with recovery of 3 cc thick pus. Both smear and culture of the material were positive for staphylococcus, coagulase positive. Antibiotic therapy was continued and a drainage procedure was not performed.

Nine days after admission the child's temperature and leukocyte count returned to normal and x-ray examination of the chest showed some decrease of pleural effusion (Figure 2). After one month of treatment with Keflex® (1.0 gm/day orally), the patient became asymptomatic and repeat chest roentgenogram showed almost complete resolution of the effusion (Figure 3).

Case 2

A 14-month-old-white female was seen in the outpatient clinic with a fever of 106°F. A diagnosis of otitis media was made and she was given Bicillin® (600,000 units intramuscularly). Four days later the patient was hospitalized because of persistent fever and shortness of breath. On examination, the respiratory rate was 80 respirations per minute with intercostal retractions and dullness to percussion and diminished breath sounds were noted at the right base. The leukocyte count was 27,400 (87% neutrophils). Chest roentgenogram revealed a right pleural effusion and infiltrate (Figure 4). Thoracentesis obtained 15 cc of green purulent fluid. Smear and culture revealed coagulase positive staphylococci. The surgical service was consulted and repeat thoracentesis removed 20 cc of pus. A drainage procedure was not done and treatment with intravenous methicillin (4.0 gm/day) was begun.

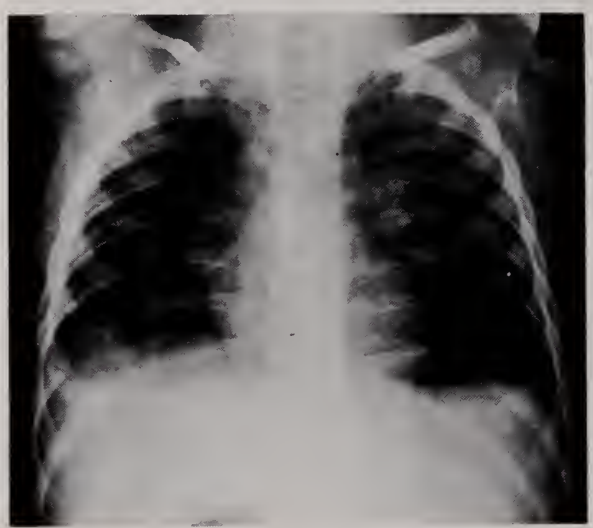


Fig. 3—Case 1. Chest roentgenogram six weeks after the onset of illness.

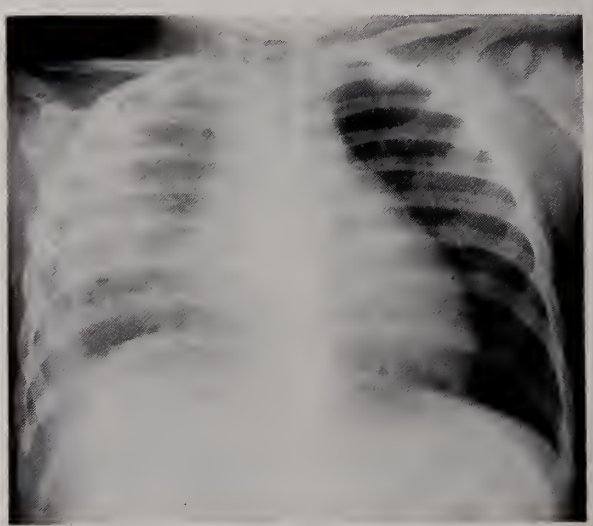


Fig. 4—Case 2. Admission chest roentgenogram showing right pleural effusion and infiltrate.

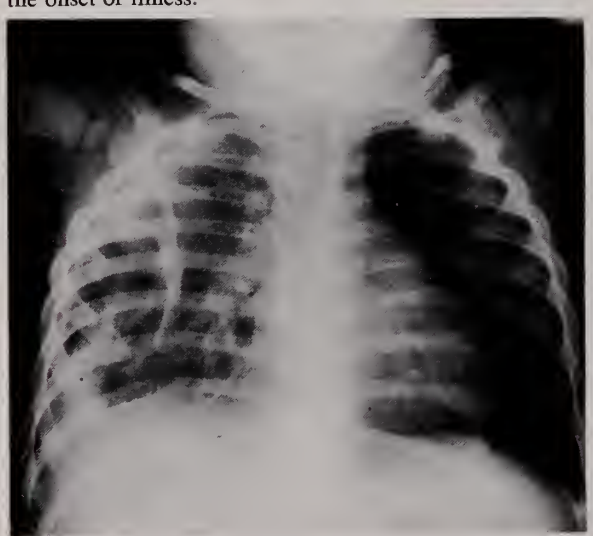


Fig. 5—Case 2. Encapsulated fluid and air seen after six days.

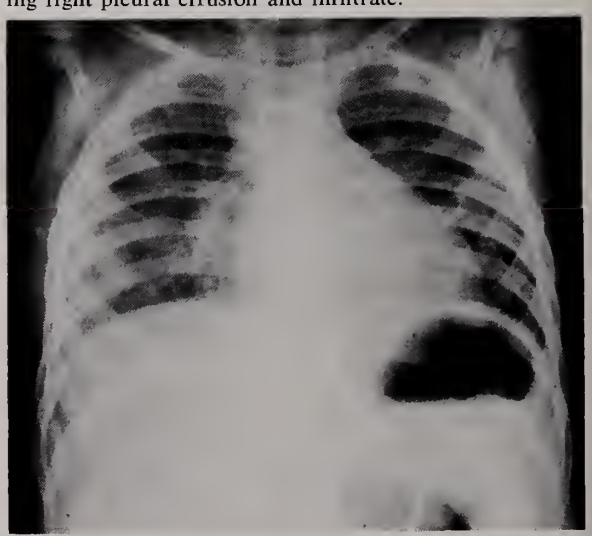


Fig. 6—Case 2. Chest roentgenogram six weeks after the onset of illness.

During the next six days the child remained febrile with an increased leukocyte count, but signs of respiratory distress improved gradually. Chest roentgenogram showed fluid with air "encapsulated" in the right pleural space (Figure 5). Methicillin was continued for two weeks at which time the child was asymptomatic; the white count had returned to normal. Another chest Xray revealed persistence of some fluid and air in the right pleural space. After three weeks the patient was discharged on oral cloxacillin (3.0 gm/day). Final chest roentgenogram two weeks following dismissal demonstrated complete resolution of the effusion (Figure 6).

Comment

As in the two cases presented, empyema occurs most commonly (> 50%) in children less than two years of age.[1,3,4] Staphylococcus, the organism in both patients, is now the causative agent in the majority of cases.[1,3-6] The patients both presented with upper respiratory infection which progressed despite antibiotics over several days, to a severe illness requiring hospitalization.

Although the empyema fluid was already thick and purulent, drainage was not instituted in either case. Instead, treatment was limited to administration of antibiotics and clinical response was monitored carefully. In both patients, the clinical resolution of the pneumonia preceded the resolution of the roentgenogram by four to six weeks.

Discussion

Stiles, et al.[6] studied the changing trends in the treatment of empyema in children at the Los Angeles Children's Hospital. They found that prior to 1962, one-half of the patients were treated with intercostal tube drainage and one-half of these were converted to open drainage, and one-quarter underwent decortication. Since 1962, tube drainage was necessary in only nine of 64 cases, with only two open drainage procedures and two decortications.

Burford, who earlier advocated an aggressive surgical approach to staphylococcal empyema, has since stressed the increased importance of antibiotics for this disease.[2] He emphasized that drainage was necessary for the staphylococcal empyema in the 1950's because the empyema resulted from a pneumonia which was resistant to penicillin. Often now the pneumonia can be controlled with specific antibiotics and with control of the parenchymal process, the pleura has shown a remarkable capacity to clear residual debris.

Pneumatocele and pyopneumothorax are occasional complications of staphylococcal empyema. The pneumatoceles result from necrotizing areas of abscess formation about the terminal bronchi. This creates an obstruction which may cause a valve-like action to develop in expiration resulting in distal air trapping and the formation of the thin walled, cystic pneumatoceles. These may rupture spontaneously, or traumatically after thoracentesis, resulting in pyopneumothorax. Tension pyopneumothorax is an urgent indication for intercostal tube drainage whenever it occurs. The natural course of pneumatoceles is slow regression and resolution over a period of weeks or months.[3]

The pleural fluid itself is variable in quantity and quality, often because of nonspecific antibiotic therapy prior to hospitalization. There may be very little fluid actually present in spite of the x-ray picture, as the opacity may represent a shaggy fibrinoid deposit between the visceral and parietal pleurae. The ultimate resolution of the pleural process is effectively accomplished by children. Occasionally as long as a year may be needed for the roentgenogram to return to normal.[5] It is postulated that greater elasticity of the lung and thoracic cage permits this to occur more readily than in adults.[5]

The roentgenographic resolution of the empyema process has been correlated with functional resolution of pulmonary physiology by Wise.[7] No evidence of altered pulmonary function or increased susceptibility to pulmonary infection was found in 15 patients studied five years after staphylococcal empyema.

Summary

Staphylococcal pneumonia and empyema in children have increased in frequency despite a decrease in the incidence of pleural empyema resulting from other organisms. Use of antistaphylococcal antibiotics during the past 10 years has reduced significantly the need for surgical drainage procedures in the management of this problem. Current treatment should be directed toward control of the inflammatory process in the lung. When accomplished the pleural empyema can be expected to resolve.

References will be found on page 382.

Presacral Dermoid Cyst

DANIEL H. DUNN, M.D.,* MANUEL BINDER, M.D.* and RICHARD HOWARD, M.D.*

Presacral dermoid cysts are rare. The classification of presacral tumors is reviewed and the clinical presentation is briefly outlined. One case report is presented, a 20-year-old pregnant woman who had an obstructed pelvic outlet. Cesarean section was necessary.

PRESACRAL MASSES ARE RARE. Only three presacral tumors were recognized in 20,851 sigmoidoscopies performed in one year at the Mayo Clinic.[14] In the same institution only one in 40,000 admissions results in this diagnosis. Swinton and Lehman[15] found 21 presacral tumors in a 28-year period at the Lahey Clinic. Other series confirm the variety of retrorectal tumors.[7,16,17] We describe here a patient with a presacral mass.

Case Report

A 20-year-old primigravida experienced a normal pregnancy until 39 weeks when it was noticed the fetal head had not descended. Pelvimetry showed adequate measurements without engagement. She underwent pilonidal cystectomy five years previously. Spontaneous labor began at term and digital examination disclosed a 12 cm, retrorectal cystic mass. The mass was partially obstructing the vaginal canal, and a cesarean section was performed with delivery of a normal male weighing 7 lb., 7 oz. Puerperium was uncomplicated, and six weeks post partum a barium enema showed deviation and compression of the rectum (Figure 1). At operation, the presacral region was entered through a Kraske incision, and a dermoid cyst was removed without complication. Postoperative course was benign.

The cyst measured 10x5x5 cm. and contained keratin debris with no calcification or teeth present. Microscopic section showed squamous epithelium and respiratory epithelium present (Figures 2 and 3).

*University of Minnesota, Department of Surgery, Mt. Sinai Hospital, Minneapolis, Minnesota.

Reprint requests to: Daniel H. Dunn, M.D., University of Minnesota Hospitals, Box 243, Mayo Memorial Building, Minneapolis, Minnesota 55455.



Fig. 1—Barium enema showing extrinsic compression on rectum with lateral deviation of rectal wall.



Fig. 2—Squamous epithelium lining wall of presacral dermoid cyst.



Fig. 3—Respiratory epithelium in one section of wall of cyst.

Classification

Lovelady and Dockerty[7] in 1948 classified presacral masses into four groups (Table). Since that time, there have been numerous attempts to simplify or to expand this classification.[10,11,15,17] Willis[18] has pointed out that a separate classification for dermoid cyst, epidermoid cyst, and teratoma is purely arbitrary and has no pathologic basis. He believes that to describe a dermoid cyst as containing only one germ layer is almost always an admission of inadequate examination, and even in the simplest cyst a proper study will reveal neural, skeletal, respiratory, or alimentary tissue. Hawkins and Jackman[5] feel that developmental cysts represent a spectrum with fetal inclusions at one end and epidermoid cysts at the other end. Spencer and Jackman[14] define precoccygeal cyst as being comprised of dermoid, epidermoid, or teratomatous elements. This has led to much confusion in the classification of presacral masses.

TABLE

Classification of Presacral Masses

- I. Congenital Anomalies
  - A. Ectopic Kidney
  - B. Teratoma
    - 1. Epidermoid cyst
    - 2. Dermoid cyst
    - 3. Complex teratoma
  - C. Meningocele
- II. Neurogenic Tumors
  - A. Neurofibroma
  - B. Ependymal cell glioma
  - C. Ganglioneuroma
- III. Bone Tumors
  - A. Osteogenic sarcoma
  - B. Chordoma
  - C. Ewing's sarcoma
- IV. Miscellaneous Masses
  - A. Myogenic
  - B. Fibroma
  - C. Inflammatory
  - D. Metastatic

There is general agreement that the clinical presentation, manifestations, and malignant potential of sacrococcygeal teratomas of infancy and presacral dermoid cysts in the adult are quite different, and there is a need for classification of these tumors on a pathologic and clinical basis. The original classification by Lovelady seems to be the most reasonable for it agrees with the general pathologic classification of teratomas but further separates these entities clinically.

Pathology

The presacral dermoid cyst contains three germ layers lined with squamous epithelium and have skin appendages, i.e., hair and sebaceous glands. These cysts are often multilocular consisting of one large cyst with several daughter cysts filled with keratin debris and cholesterol crystals. While they are usually benign, squamous-cell carcinoma has been reported in a dermoid cyst.[14,15] Most presacral dermoid cysts are found in young women;[1,4,6,8,9,13,17,18] however, they have been reported in men.[12] Melody[9] has theorized that the greater frequency in females is due to the fact that because the ovary takes 15 days longer to develop than the testis there is more time for primitive genital cells to become ectopic.

Sacrococcygeal teratomas occur most commonly in infancy and are rare in adults.[11] They contain all three germ layers but no preponderance of ectoderm. Gross et al.[3] found that malignant change occurred in 25% of 40 cases of sacrococcygeal teratomas. Sacrococcygeal teratoma and dermoid cyst may present in a similar fashion.

The third most common lesion found in the retrorectal space is the chordoma. A chordoma is a malignant tumor arising from the primitive notochord in either the spheno-occipital or sacrococcygeal region. They are slow growing, locally invasive neoplasms which cause bony erosion and have a propensity to recur following resection. They are more common in men and the average life survival after diagnosis is four years even though only 10% show distant metastases.[15]

Diagnosis

The presacral masses may cause variable symptoms including pain on defecation, constipation, sensation of pelvic pressure, partial urinary obstruction, and dyspareunia. Fifteen percent of these lesions are asymptomatic and found on digital examination or proctoscopy. Presacral cysts may become infected and present with fistulous tracts to anus, rectum, vagina, or skin. Twenty to 60% of dermoid cysts may present as infected sinuses or abscesses.[2,7,17]

Roentgenographic study of the retrorectal region should include anterior and lateral plane films of the pelvis, barium enema, and in selected cases, myelography. Plane films may show a soft-tissue mass with calcification, teeth or bone, or an anterior spinabifida which is associated with a meningocele. Barium enema shows deviation of the rectum anteriorly and often laterally by an extrinsic mass with normal mucosal pattern.

Sigmoidoscopy confirms the radiologic findings of an extrinsic mass lesion causing the rectum to deviate anteriorly. Needle aspiration of the mass from the rectal wall should be avoided since this may cause infection and sinus tract formation, while aspiration through the skin overlying the presacral mass is safer.

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Cover Sculpture

"Phylogenesis"

Dr. Don L. Carlon, practicing radiologist in Moorhead, has been doing welded sculptures for the past six years. He calls his sculpture featured on this month's cover "Phylogenesis" as it is constructed from three hip prosthesis and intended to depict the evolution of the prosthetic hips, a family group so to speak, and demonstrate the sculptural quality of a portion of the human anatomy. Even though manmade, Dr. Carlon states they emulate the real anatomy. The work is constructed of vitallium and stainless steel.

It won first place in the modern sculpture category at the American Physician's Art Association show at the 1974 American Medical Association meeting in Chicago.

Pediatric Day

May 17, 1975

"Pediatric Day sponsored by the Mayo Clinic-Mayo Foundation and arranged for by the Department of Pediatrics will be held May 17, 1975. The Amberg-Helmholz Lecture, a feature of Pediatric Day will be given by Chester M. Edelmann, Jr., M.D., Professor and Chairman, Department of Pediatrics, Albert Einstein College of Medicine. Presentations dealing with problems which occur in the practice of Pediatrics will be made by members of the staff of the Mayo Clinic and the faculty of the Mayo Medical School from the Departments of Pediatrics, Orthopedics, Surgery, Neurology, Cardiology, Radiology, and Psychiatry. For information, write Dr. E. C. Burke, Program Director, Mayo Clinic, Rochester, Minnesota 55901."

William C. Bernstein, M.D.

William C. Bernstein, M.D., emeritus director of the division of colon and rectal surgery at the University of Minnesota, has received the Clifford Emerson Hardwick Award for 1974. This is the highest honor given by the American Society of Colon and Rectal Surgeons.

Nonclostridial Crepitant Cellulitis Due to Klebsiella

MARVIN R. NAPGEZEK, M.D.* and WENDELL H. HALL, M.D.†

We report a case of crepitant cellulitis caused by *Klebsiella pneumoniae* in a 58-year-old diabetic man. Infection followed a closed fracture of the femur. The probable mode of infection was either fecal soiling of a sacral decubitus ulcer or urinary tract infection, subsequent bacteremia and seeding of the hematoma surrounding a recent femoral fracture. The patient did not survive despite a high thigh amputation, suitable antibiotics, and vigorous resuscitative measures.

NONCLOSTRIDIAL CREPITANT cellulitis can be caused by aerobic gas-forming coliform bacilli, Group A streptococci, staphylococci, anaerobic streptococci, and bacteroides species. The literature from 1940 to the present disclosed 79 cases of nonclostridial gas-forming infection of which only two cases were due to *Klebsiella pneumoniae*.[1,2] It is the purpose of this report to record an additional case of crepitant cellulitis caused by *K. pneumoniae*.

Case Report

The patient was a 58-year-old man who sustained a *closed* right femoral fracture in a fall from a wheelchair the day prior to admission. A diabetic, insulin-dependent for 20 years, he had undergone a right below-knee amputation for nonhealing ulcers in 1969, and a left above-knee amputation for gangrene in 1972.

On admission on February 11, 1974 the patient was alert and oriented with a blood pressure of 140/70, pulse 64 and temperature 97.6° orally. The skin of the right leg was not broken. Except for the previous amputations, the remainder of the physical examination showed only pallor.

Laboratory findings revealed a WBC 5,500, hemoglobin 6.8 gm% (MCV 91 μ^3, MCHC 33%), erythrocyte sedimentation rate 129 mm/hr., 4+ urinary protein. Serum calcium 5.0 mg% (N 8.5 – 10.5) phosphorus 5.4 mg% (N 2.3 – 4.5), albumin 1.9 gm% (N 3.5 – 5.3) and alkaline phosphatase 278 units (N 24-96). A chest Xray showed bilateral apical pleural thickening. An Xray of the right thigh revealed a comminuted fracture of the shaft of the femur, marked demineralization and vascular calcification. An electrocardiogram was normal.

The patient was treated with a plastic splint and a



Figure—P-A view of right thigh showing comminuted fracture of femur and numerous pockets of gas about the fracture but none in the muscle planes.

*University of Minnesota Medical Teaching and Research Unit, Northwestern Hospital, Minneapolis, Minnesota.
†Medical Service, Veterans Administration Hospital, Minneapolis, Minnesota.

Jones dressing to the right leg. He was placed on a 2,000 calorie diabetic diet, 8 units NPH insulin each A.M., and tylenol and aspirin for pain.

The first 10 days in the hospital were unremarkable except for persistent diarrhea and urinary incontinence. On day seven a broken area of skin over the coccyx was treated with a heat lamp. On day 11 the patient was found to be weak, restless but oriented, and to have a blood pressure of 76/46. He was transferred to the medical intensive care unit and underwent a respiratory arrest on arrival. He was successfully resuscitated, intubated and placed on a respirator. At this time, the laboratory reported hemoglobin 4.7, WBC 4,200 with 78% pmn, 16 stabs, four lymphocytes, and two metamyelocytes; pyuria and bacteriuria were present. His blood sugar was 390, BUN 141, sodium 144, potassium 5.7, chloride 117, CO_2 combining power 10.0; lactate 1.76 mmol/liter, pyruvate 0.13 mmol/liter, anion gap 22.7 mEq, prothrombin time 12.0 seconds (control 12.7 seconds), platelet count 337,000/mm^3. Urine test for fat was negative. He was given gentamicin 75 mg intravenously, after obtaining blood and sputum cultures.

Several hours later the patient was alert with a blood pressure of 94/50. Jaundice, petechiae and ecchymoses were absent. Coarse inspiratory and expiratory rales were heard over the anterior lung fields. The right thigh was now noted to be crepitant although not tender and the skin of the thigh was without redness or warmth. No blebs were seen. A skin break was sought but none was found. Needle aspiration of the thigh produced several drops of nonfoul, thin, serosanguineous fluid. Gram-stain revealed many Gram-negative bacilli with bipolar staining ("safety-pins"). Numerous pockets of gas about the fractured right femur were seen on Xray. (Figure).

It was felt best to treat the patient for possible clostridial infection while awaiting culture results. Three units of packed red blood cells were given. Penicillin G (10 million units daily) and chloramphenicol (1 gm I.V. every six hours) were started intravenously. He was taken to surgery. At operation there was crepitance and a large infected hematoma infiltrating the right vastus lateralis and quadriceps femoris muscles. The distal portion of the femur was amputated, and the infected muscles were removed.

Gross and histologic examination of the resected muscles showed no myonecrosis. During operation the patient was given 750 ml of plasma and 500 ml of whole blood. At the termination of surgery he had two episodes of asystole but was resuscitated with blows to the chest and external cardiac massage. Pulmonary edema was present. The patient remained afebrile until the day after surgery when a rectal temperature of 101.8° was recorded. Since blood urea nitrogen was 140 mg% and potassium now 6.4 mEq/1, peritoneal dialysis was begun. During this day two episodes of asystole occurred; resuscitation from the second episode was not successful.

Preoperative cultures of the blood, urine, sputum, thigh aspirate, and intraoperative wound culture subsequently showed pure growth of *K. pneumoniae,* sensitive to gentamicin and chloramphenicol, but resistant to penicillin. The culture produced gas from glucose under anaerobic conditions. No further cultures were taken.

Autopsy showed coronary atherosclerosis, abscesses of the prostate and right epididymis and pneumonia in the right lower lobe. There was no evidence of extension of infection in the thigh and no myonecrosis.

Discussion

Nonclostridial gas infections are most commonly due to coliform organisms, less frequently aerobic and anaerobic streptococci or staphylococci, and rarely due to bacteroides.[2,3] The probable source of infection usually is the intestinal tract.[2] Most cases of nonclostridial gas infections involve subcutaneous tissues and not the skeletal muscles. They can arise in the lower limbs of diabetic patients who have neurologic or vascular complications and frequently have poor control of their diabetes.[3,10] Notable in these infections are the absence of pain and, except for edema, the lack of skin changes in the affected area.[4,5]

Although several authors have expressed optimism about the treatment of nonclostridial gas infection with conservative surgery and antibiotics,[3,5-8] others have reported death despite adequate antibiotics and surgical drainage.[1,2,4,9]

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Waleed Amra, M.D.

Dr. Waleed Amra was elected Chief of Staff of St. Francis Hospital in Chaska; Dr. Carl Heinzerling re-elected Vice-Chief and Dr. Peter Russell elected Secretary-Treasurer.

B-Scan Ultrasound in Ophthalmology

IRVING SHAPIRO, M.D.*

B-Scan Ultrasonography is an important, non-invasive, and presently available test for clinical use as an aid to diagnosis in eye and orbit disease. A review of the present status of B-Scan Ultrasonography with examples of its application is presented in this communication.

A FREQUENCY OF SOUND waves which lies above 18,000 cycles per second is above the audible range and is termed ultrasound. In many fields of medicine ultrasound is assuming an important role. In ophthalmology ultrasound has already a secure position in terms of both research and practice and will become increasingly important in its practical applications in the near future.

This communication presents a survey of the status of ultrasound in ophthalmology today with emphasis on the practical uses of B-Scan ultrasonography.

History of Ultrasound in Ophthalmology

Henry Mundt and William Hughes recorded in 1956 the first use of diagnostic ultrasound in ophthalmology. They noted a marked pathological echogram in eyes affected with retinoblastoma and malignant melanoma.[1]

In 1957 Oksala and Lehtinen published the first observations using ultrasound in the diagnosis of retinal detachment.[2] Baum and Greenwood were the first investigators to use a two-dimensional method of ultrasound in ophthalmology.[3] Numerous publications by Coleman, Bronson, Ossoinig and many others have appeared in the ophthalmologic literature since 1967.

At a recent meeting on vitreous surgery held in San Francisco, early in 1974, Coleman demonstrated the use of color contrast in ultrasound diagnosis and Purnell showed ultrasound findings as demonstrated in moving pictures rather than still photography. Coleman has since published an article on color coding of B-Scan ultrasonograms.[4]

Biologic Effects of Ultrasound in Ophthalmology

A focused beam of high intensity ultrasound can irreversibly liquefy the vitreous in two to four seconds, cause reversible zonular like opacity in the lens in two to eight minutes and cause irreversible cortical lenticular opacities with longer exposures.

Other biologic effects of ultrasound than those noted on the vitreous and lens include the production of corneal change, ciliary body destruction and chorioretinitis. Experimental work has been done which indicates that irreversible tissue damage and reversible tissue damage are determined by time-power relationships. Generally speaking in the eye, the tissue dose of one watt per square centimeter for five minutes is the uppermost safe level.

Therapeutic Applications of Ultrasound in Ophthalmology

Ultrasound has been utilized in various clinical conditions as a therapeutic modality. These entities include pseudotumor, hyphema, anterior chamber exudate, vitreous hemorrhage and tumor destruction. Most of these evaluations in the therapeutic sense have been done without controlled studies.

Purnell and Sokollu have utilized ultrasound in retinal detachment surgery. Ultrasound has been used to push detached retinas to a different position, to change traction force on the vitreous body and to produce chorioretinitis with subsequent chorioretinal adhesion. The margin of safety between the desirable and undesirable effects, however, is small.[5]

Ultrasound has been used on the ciliary body in an effort to destroy areas of the ciliary body and produce glaucoma control. It should be noted that the ultrasound effect on the ciliary body and choroid differ from photocoagulation in that the destructive effects are not dependent upon optical properties or on the absorption of light by pigmented structures.

*Clinical Associate Professor of Ophthalmology, University of Minnesota Hospitals, Minneapolis.

Ultrasound has further been used therapeutically for localization and extraction of intraocular foreign bodies, particularly nonmetallic and nonmagnetic foreign bodies. This technique can be used for both radio-opaque and radiolucent foreign bodies.

Bronson has been particularly active in describing techniques of ultrasonic localization and extraction. He has designed an interesting forcep for use within the eye which has a 0.025 inch diameter ultrasonic crystal mounted in the jaws of the forcep.[6]

Diagnostic Uses of Ultrasound in Ophthalmology

The major use of ultrasound in ophthalmology today is in its diagnostic aspects. The A-Scan, or time amplitude scan, is a linear scan which has been useful in determining axial length of the eye and has also been useful in the diagnosis of intraocular pathology such as tumors and detachments and retrobulbar pathology such as tumor.

The B-Scan is a composite type of scan wherein multiple scans are added to give a three-dimensional view acoustically.

The so-called M-Mode echogram is achieved by utilizing an ultrasound technique wherein there is an effort made to measure dynamic change such as choroidal thickness before and after carotid compression.

Ultrasound may be utilized as a noninvasive technique to determine thrombosis, lumen width, wall thickness and elasticity of vessel wall. With the use of the Doppler transcutaneous flow indicator, the velocity of blood flow may also be determined.

This communication will make no effort to give the details of the various technical aspects of the ultrasound techniques available. Very complete references are available to the reader who may be interested in exact details of equipment, wave form and technique.[7,8]

Examples of B-Scan Ultrasound in Ophthalmology

It is important in all ultrasonic examinations to remember that there are a number of artifacts and that the two eyes should be compared. Normal acoustical landmarks must be known and clinical judgment has to be exercised.

The techniqnc of B-Scan ultrasonography as described by Bronson is simple and noninvasive.[9]

The test is done with the patient lying down and the lids closed. A small amount of sterile Methyl Cellulose solution is placed on the closed lid and a hand held ultrasound transducer is applied to the lid. The transducer itself can be moved either horizontally or vertically to get different serial sections recorded or, the patient can move the eye under the closed lid in different directions so that again different areas may be exposed to the ultrasound and thus be recorded. The acoustical wave produced is determined by the characteristics of the tissue through which the ultrasound is passing. Visualization of this acoustical wave is seen in its dynamic state on a cathode ray screen which appears like an ordinary television set. A Polaroid camera which has been pre-set and pre-adjusted to proper focus on the cathode ray screen is available and any areas of interest seen in the dynamic picture on the screen can be photographed instantly with this camera for permanent recording and later study.

Figure 1 shows a typical B-Scan ultrasound appearance. For orientation it is to be noted that the front of the eye is to the left and the back of the eye to the right. In the normal eye, the central vitreous cavity would be acoustically blank and would appear entirely black. It is to be noted in Figure 1 that midway between the front and back light areas there are small scattered white areas which represent foreign bodies in the vitreous, in this case, hemorrhage in the eye of a patient with diabetes.



Fig. 1—Vitreous foreign body.

Figure 2 again shows the lack of acoustical impedence which would be the normal vitreous cavity situation and here there are even more acoustically competent areas in the vitreous. One can begin to see a funnel-like appearance to the vitreous opacities and this funnel-like appearance

represents a detached retina with underlying organized hemorrhage. This ultrasound photograph was taken through a totally opaque cornea and thus would indicate in an eye otherwise difficult to evaluate that therapeutic efforts directed at the cornea would be of no avail because of the underlying retinal disorganization.



Fig. 2—Retinal detachment plus organized hemorrhage.

Again, in Figure 3 the central area, which should be clear, is obviously not. Again, a funnel-like entity can be visualized and in this photograph the apex of the funnel can be seen going back to the back part of the eye again demonstrating detached and disorganized retina associated with hemorrhage.

The more important reason, however, for demonstrating this photograph is to point out the distance between the front and back part of the eye as compared to the other photographs. It will be seen that the distance is much foreshortened and this gives a very good demonstration of the ability of this technique to determine the distance between the front and back part of the eye acoustically. This eye represents the eye of a youngster who has had retrolental fibroplasia. Associated with the retrolental fibroplasia there is the retinal detachment noted above and an associated lack of development of the eye as indicated by a significantly foreshortened anterior posterior diameter.



Fig. 3—Retinal detachment, organized hemorrhage plus a short eye, front to back (retrolental fibroplasia).

In Figure 4 one can see below just to the right of the anterior whiteness several areas of whiteness in the otherwise black surrounding. The most inferior of these areas of whiteness represent foreign bodies, in this case, glass within the anterior chamber. The whitened areas slightly posterior represent normal lens shadow. This picture demonstrates again the ability of ultrasound to determine foreign body, but also points out the necessity of knowing normal acoustic landmarks so that the lens shadow is not misinterpreted as foreign body.



Fig. 4—Anterior, inferior foreign body—glass.

One of the most important potential contributions of ultrasound in ophthalmology can be alluded to in examination of Figure 5. The important area in Figure 5 is at the right of the picture wherein one can see a blackish indentation in a generally white surrounding. This horizontal, slightly elongated, black surrounded by white represents the acoustic shadow of the normal



Fig. 5—Optic nerve shadow.

optic nerve as it goes through the orbital fat and surrounding orbital tissues to approach the back end of the eye.

Coleman and Carroll have evaluated optic neuropathy with B-Scan ultrasonography.[10] They have reported abnormal changes surrounding the orbital path of the optic nerve in all but one of 24 eyes with acute optic neuropathy. The changes reported were associated with acute optic neuropathy of various etiologies. Their study included eyes with clinically diagnosed optic neuropathy of multiple sclerosis, ischemia, Graves' Disease as well as other etiologies. The changes that were seen on the scans varied from faint reduplication of the nerve outline to marked doubling of the nerve echopattern and enlargement of the extraocular muscle outline. They hypothesized that the changes were edematous in nature. It was felt that the ultrasound characteristics found demonstrated evidence of inflammatory or edema-like change around the optic nerve but were not specific for a particular kind of optic neuropathy. It should be stressed again that the abnormal nerve pathway was noted as being twice as wide as the normal nerve pathway.

This ability to objectively demonstrate optic nerve disease may prove to be one of the truly exciting contributions of this technique. *"To non-invasively evaluate optic nerve disease would be a great boon to the patient."*

Summary

A survey of the current status of B-Scan ultrasonography in ophthalmology with examples of ultrasound photographs have been presented.

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Annual Meeting

The Minnesota State Medical Association's Annual Meeting is in St. Paul, May 21-23, 1975, at the St. Paul Hilton Hotel.

Ammoniated Mercury Ointment and the Nephrotic Syndrome

TERENCE J. LYONS, M.D.,* CHRIS N. CHRISTU, M.D.* and F. S. LARSEN, M.D.*

A nine-year-old patient developed the nephrotic syndrome as a result of the use of topical medication containing mercury. The relationship of this entity to other forms of mercury toxicity is discussed.

THIS PAPER DOCUMENTS mercury poisoning as the cause of nephrotic syndrome in a nine-year-old girl being treated with a 3% ammoniated mercurial base ointment over several months.

The diminishing use of mercury in pharmacologic preparations has resulted in a lower incidence of iatrogenic mercurial poisoning. With the annual consumption of mercury at over four million pounds,[1] primarily for industrial use, occupational and environmental exposure to mercury is a problem of greater magnitude. Nevertheless, mercury toxicity is still seen following the topical or systemic administration of mercurial compounds. The etiology of the nephrotic syndrome is not often idiopathic.

Case Report

A nine-year-old female was referred here for evaluation and treatment of nephrotic syndrome. The patient first noticed puffiness of the eyelids and face following a slight upper respiratory infection. Over the two weeks prior to admission she gained over 15 pounds.

There was no previous history of renal disease. An intravenous pyelogram done by the referring physician revealed a double collecting system on the right.

For the four months prior to admission, the patient had used Triamcinolone ointment in 3% ammoniated mercury base for the treatment of psoriasis.

On physical examination, the patient had generalized anasarca. She had psoriatic plaques scattered over her forehead and extremities.

There was 4+ proteinuria. The urinary sediment contained only occasional hyaline casts and red blood cells. Total serum protein was 3.6 gm.% Albumin was 0.88 mg.%. Cholesterol was 730 mg.%. The erythrocyte sedimentation rate was 73 mm. per hour. Twenty-four hour urinary protein excretion was 4,836 mg. The creatinine clearance was 95 ml. per minute. The antistreptolysin-o titer was 12 Todd units. An L.E.-cell preparation was negative. Laboratory studies also included a normal hemogram and electrolytes. The urinary excretion of mercury was found to be 244 mcg. in 24 hours (normal less than 20). This was repeated on two subsequent occasions and found to be elevated to 117 mcg. and 138 mcg. per 24 hours. Serum mercury was found to be 0.8 mcg. (normal less than 10).

The patient was treated with a low-salt diet, prednisone 80 mg. daily, and n-acetyl penicillamine 250 mg., four times daily.[2] On the eleventh day following the patient's hospitalization she began to diurese briskly. The patient lost 10 pounds in three days and was discharged with the urine containing only traces of protein. Penicillamine was discontinued after a two-week course. Steroids were gradually discontinued after two and a half months. On follow-up after five months, the patient was free of edema and free of proteinuria on routine urinalysis. The erythrocyte sedimentation rate was 2 mm. per hour and the cholesterol 130 mg.%. Twenty-four hour urinary protein excretion was 70 mg.

Discussion

The nephrotic syndrome is a well-documented manifestation of mercury toxicity. However, it is often seen in the absence of the classical symptoms and signs of mercury poisoning. The kidney is the body organ with the highest mercury concentration following absorption and is also the primary route of excretion. The fact, that (1) this manifestation of toxicity is often seen in the absence of other evidence of mercury poisoning and (2) that elevated urine and serum levels of mercury are often not found has led investigators to postulate that this may be an idiosyncratic reaction—a result of mercury hypersensitivity.[3] Seven other cases of the nephrotic syndrome attributed to the use of ointments with an ammoniated mercury base have been described.[4-7] The treatment period with the mercury-containing ointment resulting in the development of proteinuria ranged from three months to ten years. The concentration of mercury used ranged from 1% to 5-15%. In only four of these cases, however, were elevated urine levels of mercury documented. This mode of treatment for psoriasis is currently advocated in standard references,[8] although its use has been

*Department of Pediatrics, Fargo Clinic, Fargo, North Dakota.

condemned by some authoritative sources in that steroid-in-tar-base ointments are equally effective and without the potential toxicity of mercury.[9]

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Doctor George Martin—AMA Trustee Candidate



AMA Delegate Doctor George B. Martin of Thief River Falls is running for the office of AMA Trustee. He is very enthusiastically endorsed by the MSMA AMA Delegation and the MSMA Council. He has a long record of service in the Minnesota State Medical Association serving in the MSMA House of Delegates; as an alternate delegate and later delegate to the AMA; as President-Elect in 1971 and President in 1972. He is currently serving as an AMA delegate. The election for AMA Trustee will be held at the AMA Annual Meeting in June in Atlantic City.

Dr. Charles Beck, campaign manager, states that "we have an exceedingly fine candidate, and we shall do everything we can to further his election. We hope to return from Atlantic City with a new trustee."

Errata

In the list of Nominees for the Minnesota State Medical Association Offices published in the April issue of MINNESOTA MEDICINE, page 347, Dr. Rovelstad, one of the nominees for First Vice-President, should have been listed as: *Roger A. Rovelstad, M.D.*

Continuing Medical Education

The Minnesota State Medical Association in its program of Continuing Medical Education (CME) is developing a method by which all qualified sources of CME activities in the state of Minnesota may have their programs accredited. We hope that sponsors in all parts of the state will seek our assistance in providing CME activities for local physicians. On Saturday, May 3, 1975, there will be a one-day review session on the accreditation process. Attendance will be open to representatives of all sources of Continuing Medical Education in Minnesota who are interested in obtaining MSMA accreditation. The MSMA Accreditation Consultants who will be assisting applicants in the development of their programs also will be attending. It will be necessary to pre-register in order that adequate preparation may be made. Please advise the MSMA office of all representatives who plan to attend so that information concerning the program may be mailed to the person in advance.

CME Accreditation Review

Saturday, May 3, 1975

Nolte Center for Continuing Education, University of Minn.
(Church St. near University Ave., Minneapolis)
Underground parking available at Nolte Center—$1.50/Day

Minnesota State Medical Association
In Cooperation With
U of M Office of Continuing Medical Education

Participants will have read the *Pre-Survey Questionnaire* and *Accreditation Manual.*

7:30 a.m.—Registration

8:00 a.m.—Orientation Overview

8:15 a.m.—Review of Accreditation Criteria: The group will be divided into site-visitor and applicant sub-groups. Group leaders will include a physician-expert in AMA review criteria and a Health Sciences education specialist. The purpose of this session is to clarify the significance of each criterion and how, in actual application, questions in each area have been handled. The emphasis will be on audience interaction with the resource persons.

10:15 a.m.—A Case Example: The Hibbing Plan—Dr. Paul Alexander

11:00 a.m.—Skills Workshops: Three simultaneous sessions of 1½ hours each will be presented three times, permitting each registrant an opportunity to participate in each of the following workshops:

A. "Need" Assessment and Establishing Objectives—Merlin Mitchell, M.D., Mayo Clinic

B. Learning (media) Resources—David A. Garloff, Ed.D., and Marion G. Etzwiler, B.A.

C. Design of Learning Experiences (instructional methods)—Harlan Copeland, Ph.D., and staff

12:30 p.m.—Lunch—Campus Club—Provided by MSMA

1:30 p.m.—Continuation of Skills Workshops

4:30 p.m.—Summary, Discussion and Completion of Evaluation Sheet—Douglas Fenderson, Ph.D., U of M Office of Continuing Medical Education—Paul Bowlin, M.D., Chairman, MSMA Subcommittee on Accreditation

Continuing Medical Education

May

Miller-Dwan Hospital and Medical Center

Duluth Clinic Conference, May 3, Dwan Auditorium, Miller-Dwan Hospital and Medical Center, Duluth, May 3, 1975. Contact: Mrs. Linda Patterson, Miller-Dwan Hospital at (218) 727-8762, Extension 279. Conference title: "Treatment of Rheumatoid Arthritis."

American Medical Association Regional Conference

July 26 and 27, Minneapolis. Seven postgraduate courses.
Write: Department of Circulation, AMA, 535 Dearborn, Chicago.

American Board of Family Practice

Two-day written certification examination on November 1-2, 1975. Will be held at five centers in the United States. Write: Nicholas J. Pisacano, M.D., University of Kentucky Medical Center, Annex #2, Room 229, Lexington, Ky. 40506. Must file a completed application with the Board Office by June 15, 1975.

University of Minnesota

Registration information: Office of Continuing Medical Education, University of Minnesota, Box 293, the Medical School, Minneapolis 55455, or by phone (612) 373-8089.
Courses offered are:

Ophthalmology, May 5-6

The topic is Cataracts, including an up-to-date review of phakoemulsification technique and intraocular lenses.

Clinical Dermatology for Family Practitioners, May 15-17

A practical updating and review of clinical applications, enhanced by opportunity for participant discussion of problem cases.

Perinatology, May 16-17

Course content is designed to provide specific, practical guidance to physicians and nurses whose practice may include high-risk mothers and infants. This course will be held at Marshall, Minnesota.

Current Concepts in Radiation Therapy, May 28-30

The course will present comprehensive reviews in tumors of the central nervous system, breast cancer, Hodgkins Disease and the non-Hodgkins lymphomas.

Fundamentals of Clinical Hypnosis, May 30-June 1

Sponsored jointly by the Departments of Psychiatry and Family Practice, and the American Society of Clinical Hypnosis, this course offers both introductory and advanced sections.

Great Plains Organization

Meeting to be held at Ramada Inn, Bloomington, May 19 and 20. Theme for meeting will be care of perinatal patient in the community. Write: Ruth Redmond, R.N., Wisconsin Perinatal Center, 202 South Park St., Madison, Wisconsin 53715.

Metropolitan Medical Center

Neurology

Conferences, Fridays, 8:30 a.m., Center Building, Conference Room, 900 So. 8th St., Minneapolis. Contact: Mary J. Donner, Metropolitan Medical Center—338-7744.

Audio-Visual Network for Continuing Education

9:00 a.m. in Doctor's Lounge, second Tuesday of each month, 900 South 8th Street, Minneapolis. Contact: Margie Knutson, Metropolitan Medical Center, 338-7744.

Tumor Conference—Cancer

Every Monday except if a holiday. 12:00 noon, 900 South 8th Street, Lower Level Conference Room. Contact: Dr. Lyle J. Hay, MMC, 338-7744.

See other listing, pages 376 and 427

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Warnings: Patients with severe cardiac disease should be given this medication with caution. Fever and possibly heat stroke may occur due to anhidrosis.

Overdosage may cause a curare-like action, with loss of voluntary muscle control. For such patients prompt and continuing artificial respiration should be applied until the drug effect has been exhausted. Diarrhea in an ileostomy patient may indicate obstruction, and this possibility should be considered before administering Pro-Banthine.

Precautions: Since varying degrees of urinary hesitancy may be evidenced by elderly males with prostatic hypertrophy, such patients should be advised to micturate at the time of taking the medication.

Overdosage should be avoided in patients severely ill with ulcerative colitis.

Adverse Reactions: Varying degrees of drying of salivary secretions may occur as well as mydriasis and blurred vision. In addition the following adverse reactions have been reported: nervousness, drowsiness, dizziness, insomnia, headache, loss of the sense of taste, nausea, vomiting, constipation, impotence and allergic dermatitis.

Dosage and Administration: The recommended daily dosage for adult oral therapy is one 15-mg. tablet with meals and two at bedtime. Subsequent adjustment to the patient's requirements and tolerance must be made.

How Supplied: Pro-Banthine is supplied as tablets of 15 and 7.5 mg., as prolonged-acting tablets of 30 mg. and, for parenteral use, as serum-type vials of 30 mg.

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Vigorous anticholinergic action—Pro-Banthine® Vials, 30 mg., are for intramuscular or intravenous use when prompt and vigorous anticholinergic action is required.

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It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.



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addendum

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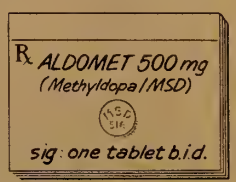
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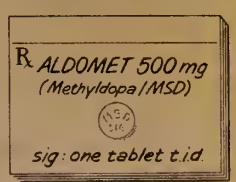
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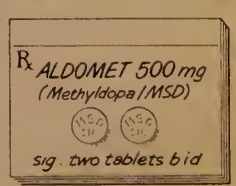
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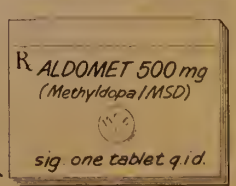


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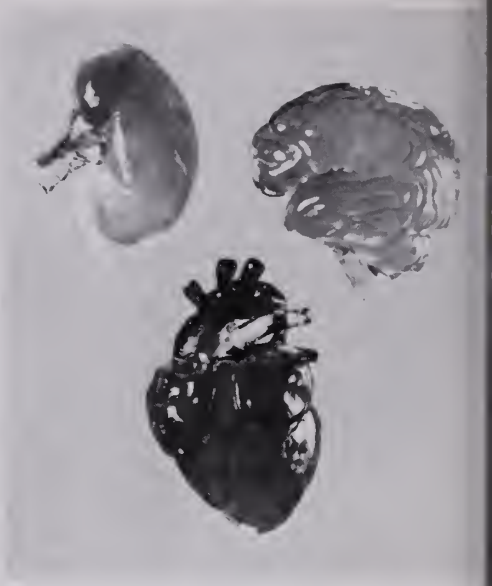


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Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis. Known sensitivity. Not recommended in pheochromocytoma. Unsuitable in mild or labile hypertension responsive to mild sedation or thiazide therapy. Use cautiously in patients with history of previous liver disease or dysfunction.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between six and twelve months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at six and twelve months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first three weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first two to three months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first six to twelve weeks of therapy or whenever an unexplained fever occurs. If fever, abnormalities in liver function tests, or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, reversible reduction in leukocyte count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur.

Use in Pregnancy and Childbearing Age—Not recommended in pregnancy. In women of childbearing age, weigh potential benefits against possible fetal hazards.

Precautions: Methyldopa may interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, spuriously high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. Stop drug if involuntary choreoathetotic movements occur in patients with severe bilateral cerebrovascular disease. Patients may require reduced doses of anesthetics; hypotension occurring during anesthesia usually can be controlled with vasopressors. Hypertension has occurred after dialysis in patients on methyldopa because the drug is removed by this procedure.

Adverse Reactions: Sedation, usually transient, m be seen during initial therapy or when dosage increased. Headache, asthenia, or weakness m be noted as early, transient symptoms. Symptor associated with effective lowering of blood pre sure are occasionally seen and include dizzines lightheadedness, and symptoms of cerebrovascul insufficiency. Angina pectoris may be aggravate Symptoms of orthostatic hypotension may occu if symptoms occur, reduction of dosage is su gested. Bradycardia, nasal stuffiness, mild dryne of mouth, and gastrointestinal symptoms includi distention, constipation, flatus, and diarrhea occ occasionally; these generally can be relieved reducing dosage. Nausea and vomiting have be reported in only a few patients. Sore tongue "black tongue," pancreatitis, and inflammation salivary glands may occur.

Weight gain and edema occur infrequently and a relieved by administering a thiazide diuretic; edema progresses or signs of pulmonary conge tion appear, discontinue drug. A rise in BUN h been observed. Other rare reactions include brea enlargement, lactation, impotence, decreas libido, skin rash, mild arthralgia, myalgia, par thesias, Bell's palsy, parkinsonism, psychic d turbances including nightmares, reversible m psychoses or depression. Urine exposed to after voiding may darken because of breakdown methyldopa or its metabolites.

Note: Dosage should be limited initially to 500 daily when following previous antihypertensi agents other than thiazides. Maximal recommend daily dose is 3.0 g. Patients with impaired ren function may respond to smaller doses than tients with normal kidney function. Syncope older patients has been related to increased sen tivity in those with advanced arteriosclerotic va cular disease; this may be avoided by lower dos Tolerance occasionally seen either early or la but more likely between second and third mon after initiation of therapy; increased dosage combined therapy with a thiazide frequently stores effective control.

How Supplied: Tablets, containing 250 mg meth dopa each, in single-unit packages of 100 and b tles of 100 and 1000; Tablets, containing 500 methyldopa each, in single-unit packages of 1 and bottles of 100.

For more detailed information, consult your M representative or see full prescribing informati Merck Sharp & Dohme, Division of Merck & Co., In West Point, Pa. 19486

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Editorials

Shigellosis

OUTBREAKS OF SHIGELLOSIS in Minnesota are a recurring problem in day care centers and institutions for children, mental hospitals, lower socio-economic areas and on Indian Reservations. In this issue an article, "Epidemic Shigellosis in Minnesota—1973"* describes a state-wide epidemic. This is the first identified state-wide epidemic of shigellosis in Minnesota involving 38 counties with a total of 1,044 cases, of which 996 were Shigella sonnei involved in this epidemic. In 1974, 32 counties were involved but there were only 370 cases, of which 317 were due to Shigella sonnei. The apparent lack of epidemic shigellosis during the past 45 years may have been an artifact because shigellosis has often been passed off as "intestinal flu"; accordingly, no stool specimens were submitted for bacteriological culture. It is almost impossible to distinguish shigellosis from other bacterial enteritis without bacteriologic culture. Also, in past years not many laboratories were prepared to culture stool specimens for shigella. Today, there are many laboratories capable of isolating shigella and a greater number of hospitals, clinics and private laboratories are referring cultures to the Health Department's Division of Medical Laboratories for definitive identification. These factors along with aggressive epidemiologic investigation make possible the identification of epidemics and hopefully the source of the disease so steps can be taken to prevent the spread. The key which opens the door to the identification of epidemics is held by the practicing physician. His requesting appropriate laboratory work to identify the etiologic agent coupled with reporting of disease to the Minnesota Department of Health makes possible a more effective preventive disease program.

Although no common source of infection was found in this outbreak, shigellosis can be prevented without such information. The keeping of shigellosis-infected feces out of food and water is often the solution to prevention of the disease. Man is the reservoir for shigella; domestic animals may harbor and disseminate the bacteria. Shigella are transmitted through the fecal-oral route from an infected person; indirectly by eating infected fecal contaminated foods, occasionally contaminated drinking water and milk; by flies or objects soiled with infected feces. Much of the prevention can succinctly be told with the "5 f's," feces, fingers, flies, food and filth. We must keep shigella-infected feces out of food, and educate food handlers and housewives as well as members of the family in the necessity of washing hands after visiting the bathroom and before and after preparing food. Education must include information on handling and protecting food against rodents, flies and other insects as well as the need to refrigerate prepared foods.

Henry Bauer, Ph.D.†
Minneapolis, Minnesota

*See page 405.
†Director, Division of Medical Laboratories, Minnesota Department of Health.

Gallium-67 Scanning for Tumor Diagnosis

GALLIUM CITRATE LABELED with gallium-67 is probably the best tumor-seeking radiopharmaceutical now available. It has been undergoing extensive clinical trials for the last few years, the largest of which is an interinstitutional cooperative study coordinated by Oak Ridge Associated Universities. Goldberg et al.* have reported their experience from the University of Minnesota Hospitals in the February issue.

Tumor visualization with gallium-67 was first reported by Edwards and Hayes in 1969. When gallium-67 was given free of carrier, it was found predominantly within the liver, spleen, kidney, and bone. The addition of stable gallium (carrier) caused a progressive increase in relative concentration within the skeleton and a relative decrease in soft tissue concentration. It was during use of this isotope in bone scans that the tumor uptake in Hodgkin's disease was first recognized.

Evaluation of a tumor-seeking radiopharmaceutical generally first requires establishment of the frequency of abnormal uptake in lesions recognizable by other diagnostic approaches. From these studies, data on specificity of uptake, target-to-nontarget ratio, and size of the smallest detectable lesion can be obtained. The study by Goldberg et al. contains such information.

The next step is to evaluate whether the use of the radiopharmaceutical would provide information for decision making not otherwise obtainable or only obtainable in association with considerable more risk to the patient. Goldberg and co-workers' data are helpful in this respect.

The experience reported by Goldberg et al. in the February issue and that of others referred to by the authors suggest that, for nonlymphomatous tumors, gallium-67 uptake is not specific enough and not consistent enough to warrant its use in the routine work-up of patients with cancer. There are exceptions, however, and Goldberg et al. present several of these. Selection of patients in whom a gallium-67 scan could be helpful in diagnosis depends on the judgment of the physician. The patients described here may serve as guidelines. In these cases, a negative scan would not exclude disease; in case of a positive scan, an inflammatory process would have to be excluded.

In contrast, with lymphomatous malignancies, results are better for certain organ systems. Goldberg et al. show excellent results in the detection of abnormal mediastinal and hilar lymph nodes. Others have shown similar data for infraclavicular lymph nodes. Since abnormal hilar lymph nodes are frequently not recognized on chest roentgenograms and since infraclavicular lymph nodes often escape detection by physical examination, the gallium-67 scan adds to the diagnostic information and appears to have a place in staging Hodgkin's disease in the chest.

Within the group of lymphomatous tumors, however, gallium-67 uptake appears to be highest in Hodgkin's disease with nodular sclerosis and lower in other lymphomas. Histiocytic cell types, including all mixed types of lymphoma, have a higher rate of positive scans than do lymphocytic types. Even in the Hodgkin's disease group, a negative scan does not exclude disease.

McCready has shown that lung parenchymal involvement by lymphoma may be seen with gallium-67 scans prior to its being recognizable on chest roentgenograms. Goldberg et al. have not confirmed this in one case (see their Table 5).

In the abdomen, scan results in the lymphomatous group are generally inferior to those reported for the chest. Both false-positive (fecal material) and false-negative scans are a problem.

Technical refinements in scanning with gallium-67 have not resulted in significantly different results. Information densities up to four times higher have been obtained by simultaneous use of two or all three major photon emissions for scanning. But as long as gallium-67 scans are not done more frequently, many nuclear medicine physicians will probably decide against the necessary investment for additional pulse-height analyzer equipment. There still is a need for more specific tumor-seeking radiopharmaceuticals.

Heinz W. Wahner, M.D.†
Rochester, Minnesota

*^{67}Gallium Scanning. Page 163, February, 1975.

†Section of Diagnostic Nuclear Medicine, Mayo Clinic.

Diagnostic Approach to Renovascular Hypertension

THAT SEVERE RENAL artery stenosis may be present in the absence of systemic hypertension has been amply demonstrated over the past several decades. The angiographic illustration of stenosis of the renal artery must be coupled with a test of function to confirm the significance of the lesion.

In the February issue of MINNESOTA MEDICINE, the article by Dr. C. R. Dunn on "Diagnostic Approach to Renovascular Hypertension"* reasserts the superior prognostic value of differential determinations of renal vein renin in predicting results of surgery for renal and renovascular hypertension. When obtained under appropriate and controlled circumstances of stimulation, renal vein renins that lateralize with a ratio of 1.5 or more to the affected or more severely affected kidney indicate potential improvement or cure after successful operation in 94% of cases.[1] Determinations of renal vein renin have clearly surpassed the value of excretory urography, isotope renography, and differential renal function studies in the "prognostic" evaluation of renal artery stenoses.[2] These tests, however, still are of considerable value in assessing the excretory and circulatory functions of the separate kidneys. In particular, these tests are highly valuable in the follow-up of patients who have renal artery stenosis, whether they are subjected to surgical therapy or to medical therapy, because renal artery stenoses, whether atherosclerotic or fibromuscular in origin may show progression in a half to a third of the patients.[3,4] Many patients with renovascular hypertension respond well to medical treatment of their hypertension and this should be considered first if, for example, surgical therapy will consist of nephrectomy because of the extent of the stenoses.

The major disagreement with Dr. Dunn in my mind is his statement that ". . . all patients who are candidates for surgical correction of hypertension must have a renal arteriogram." Such a statement would apply to the majority of the some 26 million adult Americans now considered to have hypertension! Renal arteriography is not without some risks, expense, and practical considerations that far outweigh its role in the management of the vast majority of patients, since the incidence of hemodynamically significant renal artery disease probably is 5% or less.

Clinical clues[2] to the presence of significant renal artery stenosis include the onset of hypertension in either the young or the older age group, sudden exacerbation of previously mild hypertension, rapidly progressive severe hypertension, a history of spontaneous hematuria or pain in the flank, trauma to the flank, a prolonged systolic bruit, and continuous bruits audible over the renal areas. These clinical clues should initiate further renovascular evaluation, including carefully timed excretory urography and isotope renography. If these studies are not diagnostic, then one can consider renal angiography as the next diagnostic step for the patient who has serious hypertension and is a surgical candidate from the viewpoint of his general health.

The overriding concern in renovascular hypertension is preservation of renal function as well as relief of hypertension. These two goals must be kept in mind in deciding on diagnostic and therapeutic alternatives.

Sheldon G. Sheps, M.D.†
Rochester, Minnesota

*See page 135.

†Director, Multidisciplinary Hypertension Clinic, Mayo Clinic and Mayo Foundation.

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The Wolf

LUPUS ERYTHEMATOSUS (LE)—a disease bearing a unique name which in the Latin implies the ravages of a wolf (Lupus, wolf)—has been recognized for over a century. The clinical findings may be varied with the patient presenting with symptoms referable to one or more organ systems —the skin, joints, central nervous system, serosal surfaces and kidney. It is involvement of the kidney however that has been responsible for the significant mortality and morbidity of the disease. During recent years an abundant amount of evidence has implicated antigen-antibody complexes in the pathogenesis of the vascular and glomerular injury.

Although a false serologic test for syphilis had been known to occur in LE for over a half a century, it was the observation of the LE cell in 1943 by Hargraves, Richmond and Morton at the Mayo Clinic that ultimately led to understanding certain important immunologic features of the disease. It was later shown that the development of the LE cell required the presence of a serum factor—a 7S IgG antibody with immunologic specificity for nucleoprotein—that allowed nuclear material to be engulfed by a polymorphonuclear leukocyte in the presence of complement.

Numerous subsequent studies demonstrated antibodies in sera with specificity for a variety of nuclear antigens including native DNA, single-stranded DNA, double stranded RNA as well as other cellular and protein antigens. Although anti-nuclear antibody may be present in other diseases, antibody to native DNA has been shown to have a high degree of specificity for LE. A number of techniques have been developed to detect these antibodies—indirect immunofluorescence using animal or human tissue as targets (FANA), electroimmunodiffusion, radioimmunoassay and hemagglutination—methods which are more sensitive than a simple search for the presence of LE cells. The importance of these antibodies in the pathogenesis of tissue injury—particularly lupus nephritis—has been shown by the demonstration of immunoglobulins in glomerular capillary deposits that have specificity for a number of nuclear antigens.

Glomerular damage is mediated by antigen-antibody complexes that localize in the glomerular capillaries by mechanisms which are incompletely understood. The depression in serum levels of classical and alternate pathway complement components, the occurrence of cryoglobulins and rheumatoid factor, the demonstration of serum complexes in some patients, and the presence of complement and immunoglobulins in the glomeruli having anti-nuclear specificity—all strongly implicate complex injury as a major pathogenetic mechanism.

The demonstration of antibody with nucleoprotein specificity in other sites—including the epidermal basement membrane and blood vessels as well as the depression of complement in serosal fluid—suggest that tissue damage in other sites may also be complex mediated. At present, a major dilemma in our understanding of this disease is why patients make these antibodies. Some indices of cell mediated immunity may be altered in patients with LE—findings which may indicate an imbalance between cell mediated and humoral immunity. Whether these findings are primary or secondary effects is unknown.

In the January issue of MINNESOTA MEDICINE,* Donadio and Holley concisely summarize the various types of renal disease. Since antigen-antibody complexes appear to be responsible for the glomerular injury, the factors that influence the localization in the glomerulus in LE are largely unkown. Why one patient develops minimal mesangial abnormality or membranous nephropathy and another fulminant necrotizing glomerulonephritis with crescents remains an enigma although the type of complex and its complement-fixing capacity may be important determinants.

Prior to the use of corticosteroid therapy, there was no effective treatment for lupus nephritis. The comments of Donadio and Holley regarding the use of such therapy in active lupus glomerulonephritis should be widely supported and accepted. In addition, attempts should be made to alter the abnormal immunologic features of the disease—e.g. the hypocomplementemia and high titers of DNA antibody—since reversal of these parameters generally is associated with clinical improvement.

Their recommendation to withhold aggressive therapy when glomerulitis or membranous ne-

*Donadio JV Jr and Holley KE: Lupus nephritis. 58:43, 1975.

phropathy is present may not be appropriate in all patients—especially children and adolescents—since progressive glomerular injury, vascular disease in other organs, and central nervous system involvement might develop. The ideal corticosteroid or cytotoxic therapy of LE might be that which controls systemic symptomatology as well as returning the abnormal immunologic features of the disease to as close to normal as possible. A careful balance between this idealized approach and the risks of aggressive therapy is essential.

Alfred F. Michael, M.D.*
Minneapolis, Minnesota

*Professor, Department of Pediatrics, University of Minnesota.

Computerized Transaxial Tomography

COMPUTERIZED TRANSAXIAL TOMOGRAPHY (CTT)* is one of the most exciting advances in radiology in a long while. At present, the generally available commercial equipment is for the head only, and cost plus complexity of installation limits availability. A unit that is capable of scanning other body areas, in addition to the head, will soon be installed at our University. Experience at most centers is that the demand of day-to-day patient care soon takes all available time and energy. Projects and studies designed to evaluate basic pathophysiology of the brain may have to wait until we catch up with demand and also learn the limitations and potential of the examination.

Not to be ignored are savings being realized in selected cases, not only in money, but in risk and discomfort to the patient.

As we have gained in experience with both unenhanced and enhanced (Intravenous contrast material) scans, the CTT scan is proving to be the definitive imaging procedure in an increasing percentage of cases.

H. H. Eelkema, M.D.†
St. Paul, Minnesota

*See Houser OW et al.: Recent advances in neuroradiology. 58:122, February, 1975.
†Department of Radiology, United Hospitals, St. Luke's Division, St. Paul, Minnesota.

Progress in Hodgkin's Disease*

BETTER UNDERSTANDING in the nature of Hodgkin's Disease, both in regard to extent of disease and the morphology of disease, has done much to improve the prognosis. In the early 1950's lymphangiography procedures were developed and by 1960 this became available in most general hospitals. With this we recognized that the Hodgkin's Disease process was often much more extensive than presented clinically. From knowledge that we gained from lymphangiography it became evident that often surgical exploration was necessary for further assessment of the disease process. Staging laparotomy has now become a very acceptable procedure.

The classification by histologic types has changed in recent years also. Most recently a simplified classification has been worked out which is aimed at predicting the prognosis of disease.

As we have made progress in Hodgkin's Disease we have also made progress in the other lymphomatous diseases. Some are very sensitive to radiation and some are not. Some have been responsive to combining drug treatments. As progress advances, we can look forward to improving treatment of these patients also.

John C. Kelly, M.D.
Minneapolis, Minnesota

*See Smith DG et al.: Hodgkin's Disease. MINNESOTA MEDICINE 58:157, 1975

Letters to the Editor

Dear Editors:

A year ago MINNESOTA MEDICINE carried an article* discussing the "potential" of biofeedback techniques for the control of pain. In the year since that article was published, the use of biofeedback technology in treatment settings has proliferated. Several clinics in the Twin Cities and out-state areas have been using biofeedback techniques for the treatment of a wide variety of disorders ranging from migraine headaches to chemical dependency.

In a small way, that article has contributed to the unprecedented output of publicity and literature in both the lay and professional press. This in turn has perhaps created the illusion that significant breakthroughs in treatment have already occurred. Unfortunately this is not the case.

I think it quite likely that the use of these techniques will increase for some time to come and I feel it is important that physicians and other members of the health care community be aware of the fact that biofeedback treatment procedures continue to represent only a potential and a promise. With the possible exception of electromyographic biofeedback, there are no well controlled, replicated, long-term clinical studies demonstrating the clinical efficacy of biofeedback procedures.

The problem is compounded by the fact that money for research from both public and private sources is in short supply. The money that is available is less likely to be allocated to biofeedback research as long as sensational, exaggerated, or unsupported claims for efficacy are made. These kinds of claims are encouraged by the absence of hard scientific data. Thus, the difficulties feed upon themselves.

While the phenomemon of autonomic learning and the self regulation of normally involuntary processes have been clearly demonstrated, there is at this time no reliable evidence of treatment effects beyond those which might be attributed to relaxation, placebo, or a combination of these two things. Because of its real potential, it is especially important that sound and responsible research be continued in this area. Clinical applications should be used with caution and full knowledge of what we know and do not know in this area. As professionals we do not guarantee what we sell to the public and it is therefore especially important that we be responsible and accountable beyond simply believing in the efficacy of the techniques that we use.

*Roberts, A.H.: Biofeedback Techniques. 57:167, March, 1974.

Alan H. Roberts, Ph.D.
Professor and Director
Pain Treatment Program
University of Minnesota

Dear Editors:

Is patient education effective in improving health care, and is it necessary? With timely and good patient education, certain illnesses, accidents, or exposures could be avoided, thereby curtailing some sources of drain on medical resources. A good example of this might be the diabetic patient where an intimate understanding of his disease is important to its adequate control. Other chronic illnesses appear more easily controlled and thereby lived with, if the patient understands the disease process. Hospitalization for the asthmatic should be a rare exception if the patient seeks help soon enough, but the patient must be taught to recognize when asthma is not being adequately controlled by means at hand—i.e. patient education.

Some of the benefit obtained by being an educated patient may be more difficult

to measure than blood sugars or hospital utilization. Psychological aspects may be improved through educational means. Such may be the case in teaching breathing exercises to patients with asthma or emphysema or from the various clubs that have been organized for patients who have had mastectomies, colostomies, and other surgical procedures. If a patient is made more comfortable with his illness, a significant benefit has been obtained.

Now the lay press, government agencies, HMO's and the like, would have us believe that by practicing preventative medicine we can substantially reduce the cost of health care. If we accept patient education as beneficial, it is certainly a form of preventative medicine.

The question is, who pays? At this time most services of patient education are obtained through voluntary health agencies such as the American Lung Association or the American Cancer Society, among several others, and therefore society pays through contributions. If these services are beneficial, they should be more widely offered through clinics, offices using paramedical help, and other sources of health services. But the usual means of payment then should be in effect such as third party carriers, welfare, Medicare, and of course, the patients themselves. Recently, Medicare refused to cover the cost of a breathing exercise training program prescribed by the patient's physician. If we are serious about practicing preventative medicine, these inconsistencies in availability and compensation for such services should be corrected.

S. Scott Nicholas, M.D.*
Minneapolis, Minnesota

*Clinical Associate Professor, Department of Medicine, University of Minnesota and Chairman Asthma Committee, American Lung Association of Hennepin County.

Harold A. Diehl Award

The committee for the Diehl Award given annually by the Minnesota Medical Alumni Association solicits nominations for this award from the physicians of Minnesota. The award is presented to one or more physicians meeting these four major criteria:

1. Preferably an alumnus of the University of Minnesota Medical School.
2. Not engaged in an academic capacity.
3. Has made outstanding contributions to the Medical School, the University, the Alumni Association or the community at large.
4. Have a relatively long experience in the field of medical science or a related field.

Nominations for the 1975 awards should be sent immediately to:
1, 1978)

Konald A. Prem, M.D.
Chairman, Diehl Award
Box 395
University of Minnesota Hospitals
Minneapolis, Minnesota 55455 (373-8854)

Letters to the Editor

We would like to encourage physicians to contribute to the Letters to the Editor Section. We want to hear what you have to say, what you think, why you hold certain opinions. In short, we want to make this as lively and spirited a section as possible.

The Editors

Medical Societies

The Minnesota Urological Society

On October 18th of last year, the Urologists of Minnesota met in Rochester to endorse proposed by-laws and elect inaugural officers for a new organization: The Minnesota Urological Society. This group supercedes the Twin City Urological Society. This Society has existed since the late 1920's when it served as a social gathering for Minneapolis and St. Paul Urologists. They sometimes referred to it as the "watering hole," especially during prohibition. For a time during World War II the group didn't meet regularly, but Dr. Fred Foley revived the society and they returned to the Town and Country Club where the earlier meetings took place.

Urologists were originally attracted to the fellowship and exchange of the professional and scientific advice of such men as Dr.'s Fred Foley, Frank Wright, Gilbert Thomas, Phil Donohue, Ted Sweetser, Sr. and many others.

Dr. C. D. Creevy joined the group in 1931, became Chairman and Professor of Urology at the University of Minnesota, and is still an active participant.

Many of the Mayo Clinic Urologists have been enthusiastic supporters, especially the late Dr. John Emmett, who traveled the miles to the meetings many times.

Out state urologists will now feel that they are integral members of the new State Society, and they will actively plan meetings, hold office and benefit from the continuing education programs which will satisfy both state and national requirements.

For the first time, a spokesman group will represent Minnesota Urologists in all economic and social decisions in negotiations with government and private insurance carriers and will also make peer review a cohesive procedure rather than a divisive one.

The newly elected officers include: President—Dr. Laurence Greene, Mayo Clinic, President-Elect—Dr. Warren Brooker, Duluth, Minnesota and Secretary-Treasurer—Dr. William Price, Minneapolis, Minnesota.

We welcome prospective member inquiries and invite their attendance at the meetings.

Rodger R. Lundblad, M.D.
Past President
Minnesota Urological Society

Officers of Minnesota Radiological Society

President: Harlan W. Hawkinson, M.D. (March 1, 1975-March 1, 1976).
President-Elect: Eugene Gedgaudas, M.D. (March 1, 1976-March 1, 1977).
Secretary-Treasurer: Marvin E. Goldberg, M.D. (3 year term expiring March 1, 1977)
Councilor to A.C.R.: Harry W. Mixer, M.D. (3 year term expiring March 1, 1976)
Councilor to A.C.R.: Harley C. Carlson, M.D. (3 year term—March 1, 1975-March 1, 1978)
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rnings: Do not use dietary potassium supplements potassium salts unless hypokalemia develops or tary potassium intake is markedly impaired. teric-coated potassium salts may cause small wel stenosis with or without ulceration. Hyperlemia (>5.4 mEq/L) has been reported in 4% of tients under 60 years, in 12% of patients over years, and in less than 8% of patients overall. rely, cases have been associated with cardiac irgularities. Accordingly, check serum potassium ring therapy, particularly in patients with susted or confirmed renal insufficiency (e.g., elderly diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect.

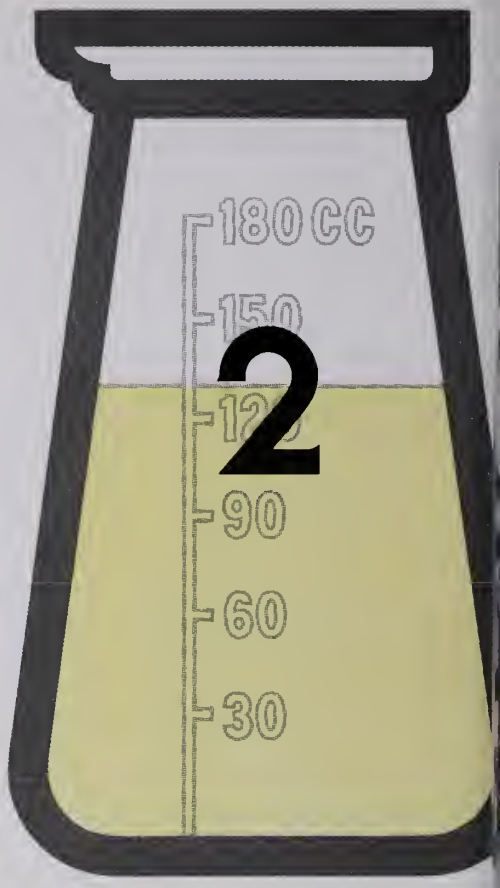
Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Rarely, necrotizing vasculitis, paresthesias, icterus, pancreatitis, and xanthopsia have occurred with thiazides alone.

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Contraindications: Sulfonamide hypersensitivity; pregnancy at term and during nursing period; infants less than two months of age.

Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

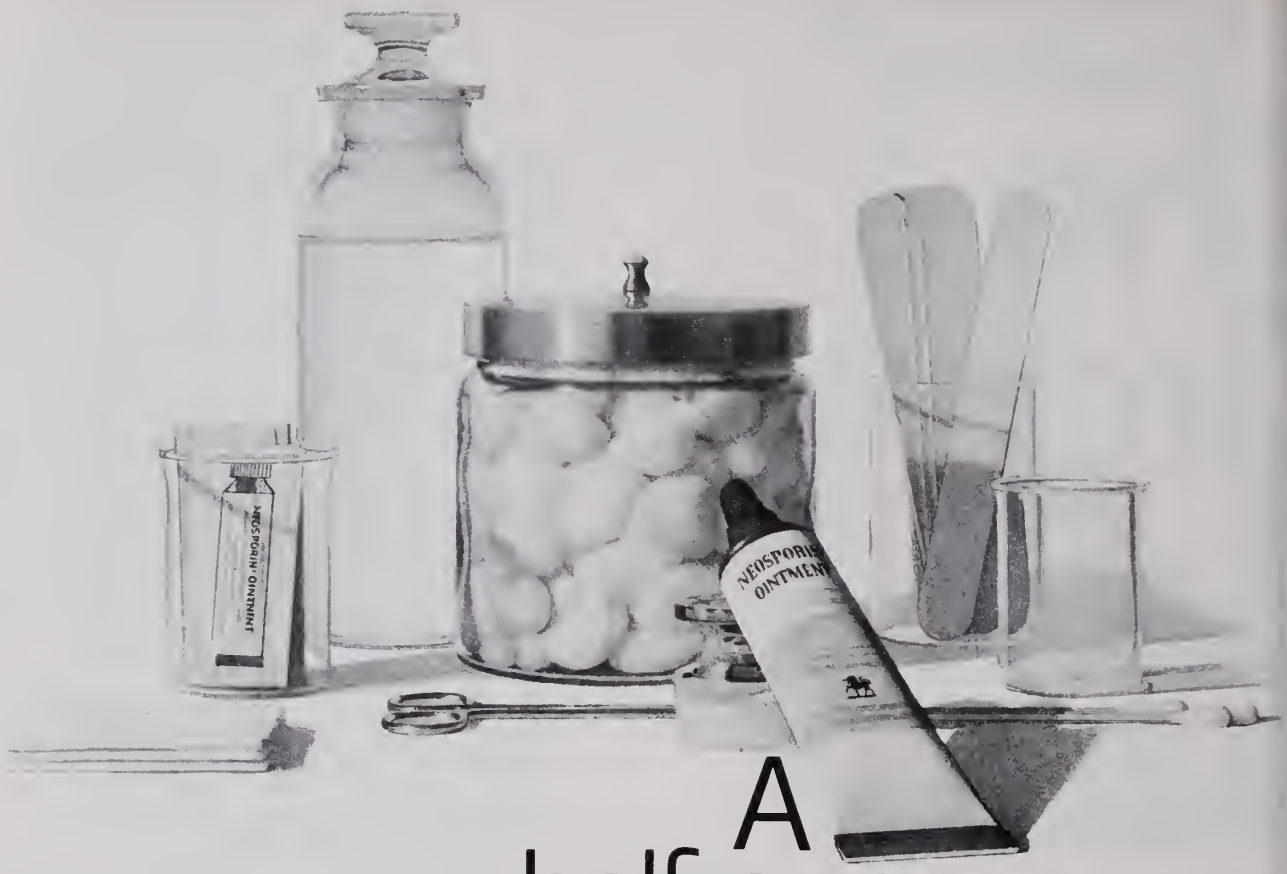
Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

Supplied: Tablets, 0.5 Gm sulfamethoxazole; Suspension, 0.5 Gm sulfamethoxazole/teaspoonful.

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(polymyxin B-bacitracin-neomycin)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs.
In tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

INDICATIONS: *Therapeutically,* used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.

Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent o body surface is affected, especially if the patient has impaired renal functi or is receiving other aminoglycoside antibiotics concurrently, not more tha one application a day is recommended.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropr measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of p allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

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Minnesota Health Department

Epidemic Shigellosis in Minnesota
1973

BARRY S. LEVY, M.D.,* JACK B. WEISSMAN, M.D.† and TOM EDWARDS, M.D.†

A large statewide epidemic of *Shigella sonnei* enteritis in Minnesota was first recognized when the number of reported culture-proven cases increased six-fold in the second quarter of 1973. A total of 996 culture-proven cases occurred in the state during the year, 23 times more than during 1972. Approximately half of these cases were in children under 10 years of age. Forty percent of the cases occurred in Minneapolis, where many cases were initially clustered in a low-income area. More than 95 percent of the organisms were resistant to ampicillin, tetracycline, and streptomycin. Almost one-third of those ill were treated with antimicrobials. Although illness was usually relatively mild, 61 (21 percent) of the first 292 Minneapolis cases were hospitalized. No common source of infection was found.

A LARGE SHIGELLOSIS epidemic occurred in Minnesota in 1973, affecting primarily residents of Minneapolis. This investigative report of that epidemic is relevant because epidemic shigellosis is becoming more frequent in American cities. Epidemics have been reported recently in Cleveland,[1] Lexington (Kentucky),[1] New Orleans, and several other urban areas.

The Minnesota epidemic was first recognized in July 1973, when the number of reported culture-proven cases of *Shigella sonnei* enteritis was found six times greater in the second quarter of the year than in the previous nine quarters (Figure 1). (In 1971 and 1972, there had been no seasonal changes in incidence.) Most of the cases in the second quarter of 1973 were in Minneapolis residents. In retrospect, it was noted that a slight increase in the number of culture-proven cases occurred in March and that this increase remained stable until June, when a sharp upsurge began. By July 28, 333 positive *S. sonnei* cultures had been confirmed by the state laboratory for 1973, as compared with 44 for all of 1972 and 140 for 1971, and an intensive investigation was begun, primarily by epidemiologists of the Minnesota Department of Health and the Center for Disease Control (CDC).

Methods

Surveillance of Shigellosis in Minnesota

Routine surveillance is based on reports of cultures positive for *Shigella* from the Division of Medical Laboratories, Minnesota Department of Health (state laboratory). Some positive cultures

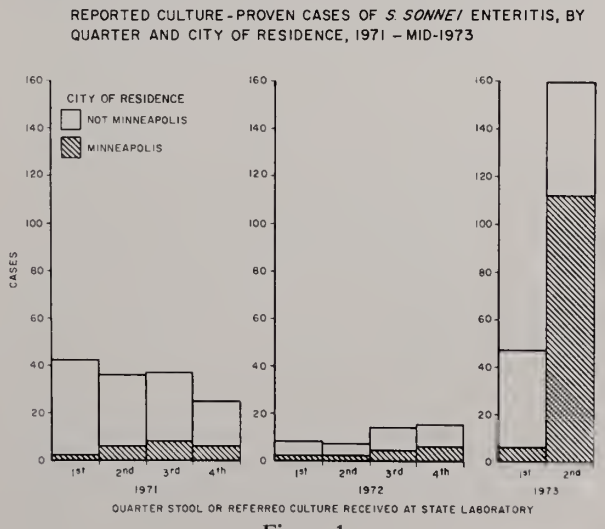


Figure 1

*Division of Personal Health Services, Minnesota Department of Health, and the Field Services Division, Bureau of Epidemiology, Center for Disease Control.

†Bacterial Diseases Division, Bureau of Epidemiology, Center for Disease Control, U.S. Department of Health, Education, and Welfare. Dr. Edwards was a fourth-year student at Emory University School of Medicine at the time of his participation in this investigation. Dr. Weissman is currently a senior resident in medicine at Columbia-Presbyterian Medical Center, New York, and Dr. Edwards, an intern in family practice at John Peter Smith Hospital, Fort Worth, Texas.

Reprint requests address to: Dr. Levy, Minnesota Department of Health, 717 Delaware Street, S.E., Minneapolis 55440.

See editorial, page 393.

are from stool specimens mailed in directly, but most are referred to the state laboratory from other clinical laboratories, which generally refer suspected enteric pathogens (including *Shigella*). Laboratory reports, which include name of patient, age, sex, address, and organism isolated, are reviewed by epidemiologists each week to detect any unusual change in incidence or case clusters that may have occurred.

Epidemic Investigation

As noted above, routine surveillance suggested the occurrence of an epidemic. Total numbers of state laboratory enteric cultures and of those positive for *S. sonnei* were reviewed to rule out the possibility that this apparent epidemic was an artifact of increased culturing or reporting.

In order to elucidate the epidemiology of the outbreaks, several studies were performed, each with slightly different time periods.

In late August 1973 appropriate data were abstracted from the laboratory reports of all 243 culture proven cases in Minneapolis that had by then occurred. Attack rates by age, sex, and census tract were calculated on the basis of 1970 census data. The latter were correlated with median income, percentage of children under five years of age, and median number of persons per household for each census tract. Times of receipt of positive culture specimens by the state laboratory, which were shortly after times of onset of illness in most cases, were plotted chronologically on an epidemic curve, and places of residence of Minneapolis cases were plotted geographically on a pin map. Antibiogram reports were obtained from the two hospitals that had submitted the most positive cultures to the state laboratory. In an attempt to obtain more information about possible modes of transmission, many physicians, nurses, sanitarians, staff members of several day-care centers and other facilities for children, as well as patients and their families were interviewed. Several possibilities were investigated in an attempt to explain the onset of the epidemic in early spring. No detailed investigation, however, was performed to detect a specific potential foodborne or waterborne mode of transmission.

To obtain more information on illness, secondary spread, and factors affecting transmission, a survey was performed of the 55 Minneapolis households where 60 individuals with *S. sonnei* infections which had been confirmed between July 23 and August 22 lived. Epidemiologists and other health workers from city-state health departments and CDC attempted to interview a responsible, knowledgeable individual in each of the households and were able to contact such a person in 51 of the 55 households, 41 in person and 10 by telephone. The name, age, and sex of each household member was recorded, along with usual bedroom-, bed-, and bathroom-sharing arrangements; recent occurrence of fever, diarrhea, abdominal pain, tenesmus (defined here as "a sense of urgency to move one's bowels"), nausea or vomiting, headache, or other symptoms in each family member; date of onset of illness and total duration of symptoms; antimicrobial, antidiarrheal, and other treatment; and, for each household member, daytime care (defined as "day-care center (including nursery school) attendance" and/or "informal day care" not in such a facility but away from home), other group contact, and recent contact with anyone who had diarrhea. No attempt was made in this survey to identify any infected individuals among those who were asymptomatic.

An apparently high rate of hospitalization among culture-proven Minneapolis cases led to the concern that organisms of increased virulence may have been causing the epidemic. To further define the clinical course of these cases, a survey of all Minneapolis residents hospitalized because of *S. sonnei* enteritis between January and early September, 1973, was performed by one of the epidemiologists (B.L.) between August 27 and September 7. Sixty-eight patients were identified at the six Minneapolis hospitals that had reported almost all of the hospital-associated cases. One additional hospitalized patient was identified from household survey data. Eight of these 69 patients were not considered in the analysis because they were not Minneapolis residents or not hospitalized primarily for shigellosis. Records were available for 52 of the remaining 61 patients, and name, age, sex, address, hospital, dates of admission and discharge, admitting and discharge diagnoses, duration of symptoms before admission, chief complaint and other symptoms prior to admission, recent contact with individuals with diarrhea or specifically shigellosis, abnormal physical findings on admission and peak temperatures and white blood cell counts were abstracted from each of them. No data could be obtained retrospectively to measure the effectiveness of antimicrobial treatment.

Laboratory Studies

Antibiotic sensitivities of organisms were determined by laboratories at two Minneapolis hospitals and CDC, using the single disk method of Kirby and Bauer.[2] Colicin typing was performed by the Epidemiologic Services Laboratory, CDC, using a method modified from that of Abbott and Shannon.[3]

Results

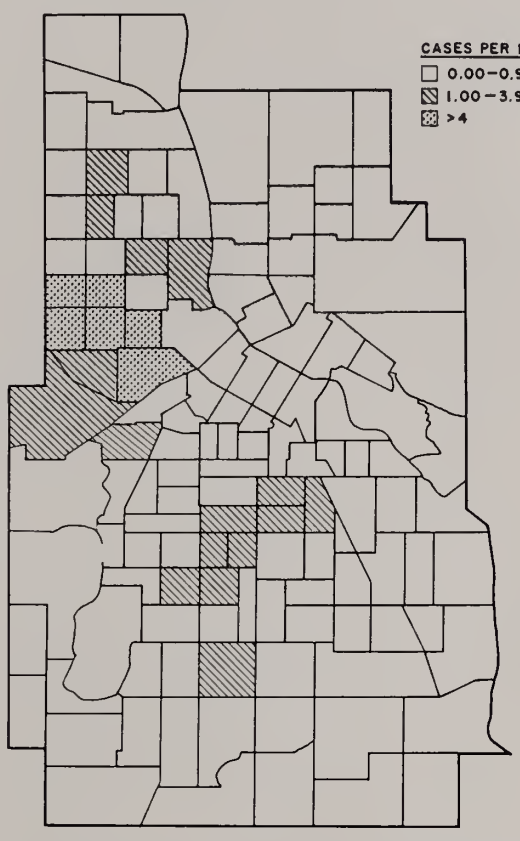
Preliminary investigation in August revealed that almost two-thirds of the 333 *S. sonnei* isolates confirmed at the state laboratory in 1973 were from stools of Minneapolis residents, and that approximately half of these were from residents of a 3.4-square-mile, low-income area on the north side of the city; this area had a relatively high percentage of young children. The other cases were reported from throughout the rest of the state. Most cases were in children. A common source of infection was not evident, and the circumstances accounting for the slow onset of the epidemic in March and the sudden upsurge in June were not readily apparent. Physicians interviewed suspected person-to-person transmission as the primary means of spread. Many children at two of the 108 registered day-care centers in Minneapolis had shigellosis, necessitating both centers to be closed temporarily, and there were reports of cases in children attending other day-care centers, summer camps, and community centers.

The increased number of cases did not appear to be an artifact caused by a change in reporting or culturing practices. The number of stool specimens sent directly to the state laboratory for culture and the number of all enteric cultures sent there by other laboratories for confirmation showed only slight increases as compared with numbers submitted in previous years. The percentage of stools sent there directly that were positive for *S. sonnei*, however, rose from 0.6 in 1972 to 4.3 in the first half of 1973, and the percentage of enteric cultures sent there from other laboratories from 2.3 to 29.3. Several physicians from the north side of Minneapolis reported that they were seeing substantially more cases of acute gastroenteritis than they had diagnosed in previous summers.

Minneapolis Cases

The highest attack rates, between 4.8 and 8.4 cases per 1,000, were in six contiguous census tracts on the north side of the city (Figure 2). Sixteen census tracts had rates between one and four cases per 1,000, and 45 others had cases but rates less than one case per 1,000. Fifty-five census tracts had no cases. The correlation coefficient for census tract attack rates and median

CULTURE-PROVEN *SHIGELLA SONNEI* ENTERITIS ATTACK RATES, BY CENSUS TRACT,* MINNEAPOLIS, JANUARY – AUGUST, 1973



* FIVE CENSUS TRACTS WITH POPULATION LESS THAN 1000 WERE EXCLUDED FROM THE ANALYSIS ON WHICH THIS MAP IS BASED

Figure 2

TABLE 1

Characteristics of Census Tracts by Attack Rates Based on Numbers of Culture-Proven Cases of S. Sonnei Enteritis Reported, Minneapolis, 1973 (Through August 24)

Attack Rate (Cases per 1,000) in Census Tract	Number of Census Tracts*	Median Annual Income	Median Percentage of Population Under Age Five Years	Median Number of Persons per Household
0	55	$9732	7.0	2.3
0.01-0.99	45	9337	7.5	2.3
1.00-3.99	16	8692	8.8	2.2
4.00-8.35	6	6315	12.0	2.9

*Five census tracts with populations of less than 1,000 people were not included in this analysis.

annual income was −.33, and for census tract attack rates and percentages of children under age five was .52 (Table 1). The six census tracts with the highest attack rates had a much higher median number of persons per household than the others.

Index Case Search

Twenty-one culture-proven cases occurred in Duluth, 160 miles north of Minneapolis, in March at the start of the statewide epidemic. Almost all of these were related to an apparently localized outbreak at a day-care center. Few cases occurred in Duluth subsequently, and it was not possible to trace transmission from these cases to cases in Minneapolis, where the majority occurred in each of the following four months. Three other possibilities were considered for introducing cases into Minneapolis in March and April:

1. Two of 164 Minneapolis area residents who visited Brazil in early March returned with culture-proven *S. sonnei* enteritis. Although many others had diarrhea during the trip, these were the only two with known shigellosis. Most of these people, however, lived in Minneapolis suburbs, and none lived in north Minneapolis.
2. Two young children who had previously resided in northern Minnesota were abandoned in Minneapolis, where they were found to have shigellosis in early April. Shortly after their treatment began, they were placed in an overcrowded home for foster children in south Minneapolis where others became ill.
3. Five children at a residential school for the mentally retarded, 20 miles southwest of Minneapolis, were found to have shigellosis in April. The index case there was in a child whose family had recently returned from Mexico with culture-proven *S. sonnei* enteritis. The staff and residents at the school have much contact with Minneapolis residents.

For none of these three possibilities could a clear-cut pattern of transmission be traced to explain the onset of the epidemic in Minneapolis.

Household Survey in Minneapolis

In addition to 56 culture-proven cases in the 51 households surveyed, there were 99 clinical cases. Few of these patients' stools had been cultured. Their symptoms closely paralleled those of the culture-proven cases (Table 2). Including these clinical cases, 155 of the 245 residents of the households surveyed were affected. Most common symptoms were diarrhea, fever, tenesmus, and abdominal pain or cramps (Table 2). Illness was often relatively mild and "flu-like." The two youngest age groups, 0-4 and 5-9 years, had the highest overall, initial, and secondary attack rates (Table 3). Individuals in these age groups most often introduced illness into households. The median secondary attack rate in the survey house-

TABLE 2
Shigellosis Symptoms, Household Survey, Minneapolis, August, 1973

	Percent with Symptom		
	Culture-Proven Cases	Clinical Cases	Total
Diarrhea:	100	93	95
with blood	33	22	27
with mucus	38	18	26
Fever	85	76	79
Tenesmus*	73	80	78
Abdominal Pain or Cramps	90	66	75
Headache	65	59	61
Nausea or Vomiting	61	53	56

*During interviews in this survey, tenesmus was defined as "a sense of urgency to move one's bowels."

TABLE 3
Age and Sex Analysis, Shigellosis Household Survey—Minneapolis, August, 1973

Age in Years	Number in Group	% of Total	Number in Group ill	% in Group ill	% of Total ill	INITIAL CASES Number	% of ill in Group	% of Initial Cases	Secondary Attack Rate
0- 4	58	24	52	90	34	26	50	44	81
5- 9	41	17	35	85	23	16	46	27	72
10-19	62	25	27	44	17	8	30	14	35
20-29	45	18	27	60	17	5	19	8	55
30-39	21	9	8	38	5	3	38	5	28
40+	18	7	6	33	4	1	17	2	29
Sex									
Male	112	46	71	63	46	32	46	54	49
Female	133	54	84	63	54	27	32	46	54
TOTAL	245	100	155	63	100	59	38	100	51

holds was 44 percent. Fifty-one percent of those who lived in households where there was initially one ill person became ill. The median length of illness was five days. The median peak temperature was 103° F. among those who had their temperature taken. Among all those ill, including some who did not consult a physician, 31 percent were treated with antimicrobials and 52 percent with non-specific anti-diarrheal agents, such as Lomotil®, Kapectate®, and paregoric.*

Household attack rates did not correlate with the number of persons living in a household, nor with the number of people sharing a bedroom, bed, or bathroom. The median number of persons per survey household was four, and 45 of the 51 households had an average of less than one person per room.

Among the initial cases in each household, 49 percent had had contact with someone outside their household with diarrhea shortly before illness; among those not ill, 25 percent had had such contact in the six weeks before interview. Among those under age five, the group with the most daytime care, illness was not significantly associated with daytime care, nor with day-care center attendance or informal day care alone. Twenty-seven (87 percent) of the 31 children with daytime care as compared with 33 (89 percent) of the 37 children without daytime care had been ill. Among those under age five who had initial cases in their households, 52 percent had daytime care; among those in this age group who had secondary cases, 40 percent had daytime care ($p > .05$).

Study of Hospitalized Patients in Minneapolis

The 61 patients identified represented 21 percent of all reported Minneapolis cases as of early September. Records available for 52 of them indicated that the number of admissions chronologically paralleled the number of reported cases in Minneapolis. Two physicians hospitalized 20 (38 percent) of these patients. Twenty-five (48 percent) resided in seven census tracts with high attack rates.

Most became ill within 24 hours before admission. A history of recent contact with the disease was noted in the record of 19 patients; not all were specifically questioned, however. Symptoms and findings at time of admission are summarized in Table 4. The admitting diagnosis for most was gastroenteritis of unknown etiology, but for four it was probable acute appendicitis. The median hospital stay was five days (range: one to 18 days); younger patients generally stayed longer. The median peak temperature was 103.0° F.; 43 of the 52 patients defervesced within one day of admission. The median peak white blood cell count was 12,200. Surgeons evaluated many patients, but no operations were performed. There were no deaths. According to information in hospital records, enteric precautions were specifically ordered for only 13 (25 percent) of the 52. Forty-one (79 percent) were treated with antimicrobials, usually before stool culture results were known. (For 18 (35 percent) of the 52, stool culture results confirming the diagnosis were not available until after discharge.) Ampicillin (for 23) and sulfasoxazole (for 18) were most commonly used (eight received both). Only 12 were directed to continue antimicrobial treatment after discharge. Nineteen (37 percent) of the 52 received non-specific antidiarrheal agents.

TABLE 4
Symptoms and Findings at Time of Admission for 52 Hospitalized Patients Studied

Commonest chief complaints:	
Diarrhea	63%
Abdominal pain or tenderness	19%
Fever	12%
Commonest symptoms prior to admission:	
Diarrhea (with blood, 17%)	73%
Fever	71%
Nausea or vomiting	56%
Abdominal pain or cramps	52%
Headache	23%
Anorexia	17%
Back pain	13%
(There was no correlation between specific symptoms and specific age groups.)	
Commonest physical findings:	
Tender abdomen	33%
Dehydration (moderate or severe, 13%)	19%
Mental status changes (lethargy, 10%)	13%
Median admission temperature	101.9°F.
Median admission white blood cell count	11,300

Laboratory Studies

Fifty of 51 *Shigella* isolates from patients hospitalized in Minneapolis were of "untypable" colicin patterns; one was type 6. Antibiograms of these isolates were:

Resistant to tetracycline, streptomycin, and ampicillin—45,

Resistant to tetracycline and ampicillin—1,

Resistant to streponycin and ampicillin—1,

*Trade names are provided for identification only, and inclusion does not imply endorsement by the Public Health Service, the U.S. Department of Health, Education, and Welfare or the Minnesota Department of Health.

Resistant to streptomycin alone—3,
Multiply sensitive—1.

Review of laboratory records at two Minneapolis hospitals in August and November revealed that more than 95 percent of isolates were resistant *in vitro* to ampicillin, streptomycin, and tetracycline, but sensitive to sulfasoxazole, chloramphenicol, and other antimicrobials. The few *S. sonnei* isolates with known antibiograms in previous years had all been multiply sensitive.

Subsequent Course of the Epidemic

The number of culture-proven cases in the state in September and October was lower than in July and August but was much higher than the number usually present (Figure 3). Fewer cases and a lower proportion of cases occurred in Minneapolis in these months as compared with the preceding three months. Several additional small clusters of cases were reported among children at facilities for the mentally retarded and at day-care centers, but the majority of cases were not associated with such facilities. In November, there was another sharp upsurge of reported cases, primarily due to an outbreak in Winona, 118 miles southeast of Minneapolis (Figure 3). Local physicians who investigated that outbreak could detect no common source of infection. In December, there was another decrease in reported cases, but the number was still much higher than usual. A total of 996 reported culture-proven cases of *S. sonnei* enteritis occurred in the state in 1973, 40 percent in Minneapolis residents, 15 percent in St. Paul residents, 11 percent in Winona residents, and five percent in Duluth residents. There were no known shigellosis-associated deaths in the state during the year.

Control Measures

The Minnesota Department of Health informed the public, mainly through newspaper articles, of the epidemic and of the need for good hygiene and sanitation. In August and November, the Department mailed practicing physicians and public health nurses reports that described the epidemic and current recommendations on isolation, hygiene, and treatment. Since shigellae were multiply resistant and were usually causing a relatively mild, self-limited illness, it was recommended that antimicrobial treatment be reserved for those few who were seriously ill and those prone to become seriously ill (infants, the elderly, and those with significant underlying disease). It was also suggested that non-specific antidiarrheal agents be avoided. Consultation was provided to physicians and to the staffs of several day-care centers and facilities for the mentally retarded which had clusters of cases.

Discussion

Four aspects of this shigellosis epidemic merit special consideration: its overall size, transmission of infection, the hospitalization rate in Minneapolis, and the multiple antibiotic resistance of the organism.

Size

Almost 1,000 Minnesota residents had cul-

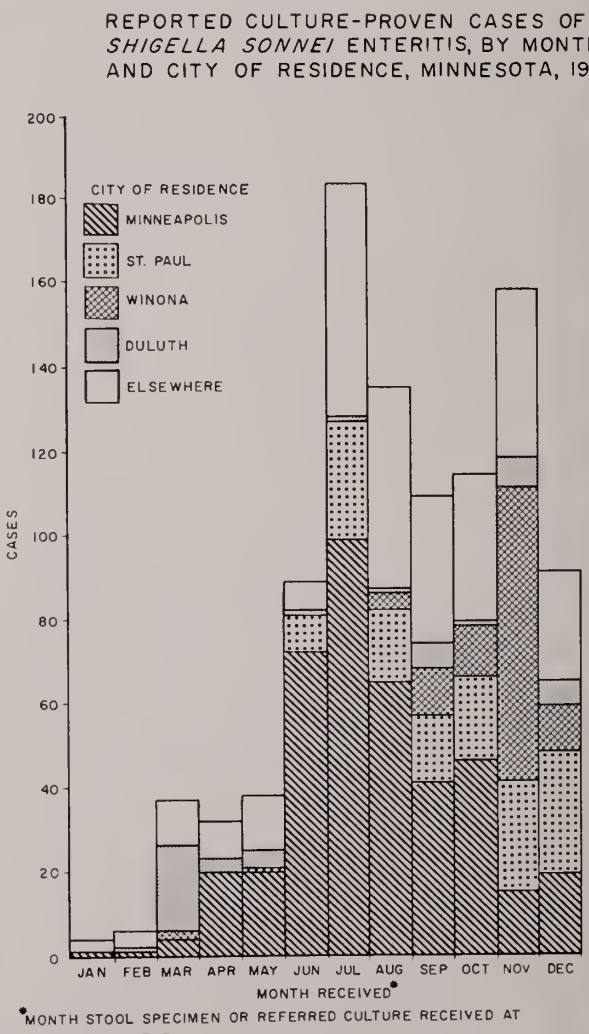


Figure 3

ture-proven cases of *S. sonnei* enteritis reported during this epidemic, but the actual number of cases was probably far greater. In Minneapolis, where 40 percent of the reported cases occurred, the actual number of people affected was probably at least three times the number of reported culture-proven cases. This figure is based upon the household survey data which identified an additional 99 clinical cases in 51 households with 56 recent culture-proven cases. The inclusion of asymptomatic infections in these households and all infections in households where no cultures were done would probably greatly increase the actual number of infections. It is likely that more than 3,000 Minnesotans had *S. sonnei* infections in 1973.

It is not clear why there were so many more cases in Minnesota in 1973 than in previous years. This increase was not an artifact since there were no known changes in laboratory or reporting practices. There was no apparent introduction of numerous cases from elsewhere and no discernible common source of infection. There was no known significant change in interaction among young children, such as an increase in the number of registered day-care centers. Certain patterns of transmission of the organism or its inherent transmissibility, however, may explain part of this increase.

Transmission

As in most reported shigellosis epidemics, transmission was thought to be primarily by person-to-person spread.[4-6] Reasons for the onset of this epidemic are unknown. Importation into the Minneapolis area of a few cases from Mexico and Brazil in March and April conceivably could have accounted for other cases. Convincing evidence of this, however, is lacking. Organisms from the Duluth outbreak in March conceivably could have been transmitted to the Minneapolis area and elsewhere in the state, but there is no evidence of this either.

The reasons why this epidemic occurred in 1973 and not in other recent years are not clearly understood. A threshold number of endemic cases in Minneapolis may have occurred in the low-income, North side area which had the highest attack rate. Increased transmission there may have been associated with the high percentage of young children in that area or with poor hygiene and inadequate sanitation, often accompanying low income, as others have shown.[4,6-8] These factors however, were not apparent and there was little evidence of crowding in the involved households. Another possible explanation is that the *Shigella* strain responsible for illness in this epidemic may have been more easily transmitted or more durable in the environment than those encountered in Minnesota in previous years.

Hospitalization Rate

The 61 Minneapolis residents hospitalized with shigellosis by early September represented 21 percent of all *reported* culture-proven cases from Minneapolis by that time. (Hospitalization rates for shigellosis in Minneapolis in previous years are difficult to obtain.) This hospitalization rate is similar to the 21 percent hospitalized in a shigellosis epidemic in Lexington, Kentucky, in 1972-1973, and the 18 percent hospitalized in another in Omaha, Nebraska, in 1961-62.[1,6] One must be cautious in making such comparisons. Moreover, hospitalization rates based on denominators of the actual number of cases, including probable cases from which cultures were never obtained, are much lower. The relatively favorable hospital-bed-to-population ratio in Minneapolis and perhaps the preference of two Minneapolis physicians to hospitalize 20 (38 percent) of the 52 patients studied may have accounted for more admissions than expected during the epidemic. It is possible, that this 21 percent hospitalization rate reflects more-severe illness, possibly explained by a more virulent strain of *S. sonnei*. A mechanism for such increased virulence, if it actually occurs, is not apparent, though some have suggested that an R factor of *Shigella* and other enteric pathogens enhances their virulence in addition to conferring multiple drug resistance.[9]

Multiple Antimicrobial Resistance

The multiple resistance of *S. sonnei* organisms to ampicillin and other commonly used antimicrobials in this and other recent shigellosis epidemics[10-13] is of great concern. Although we have not attempted to prove that antimicrobial resistance in organisms in this epidemic is episomally mediated, it is likely that the majority of organisms resistant to ampicillin, tetracycline, and streptomycin contained an R factor for resistance to these antimicrobials. The use of antimicrobials in treating even mild cases (household survey data indicated 31 percent of those ill received antimicrobials) may be selecting out such multiply re-

sistant organisms.

Control measures in this epidemic were primarily educational and advisory because the vast majority of cases were relatively mild and self-limited. Recommendations sent to physicians stressed the need to restrict antimicrobial treatment to those few who were severely ill or prone to become severely ill. Recommendations also cautioned against the widespread use of non-specific anti-diarrheal agents which decrease intestinal peristalsis.[14]

Final Note

By the end of 1973, the number of newly reported cases was declining, but it still was uncertain whether the incidence of *S. sonnei* enteritis would return to its original low endemic level in Minnesota. In 1974 there were only 317 reported culture-proven cases of *S. sonnei* enteritis in Minnesota.

Acknowledgments

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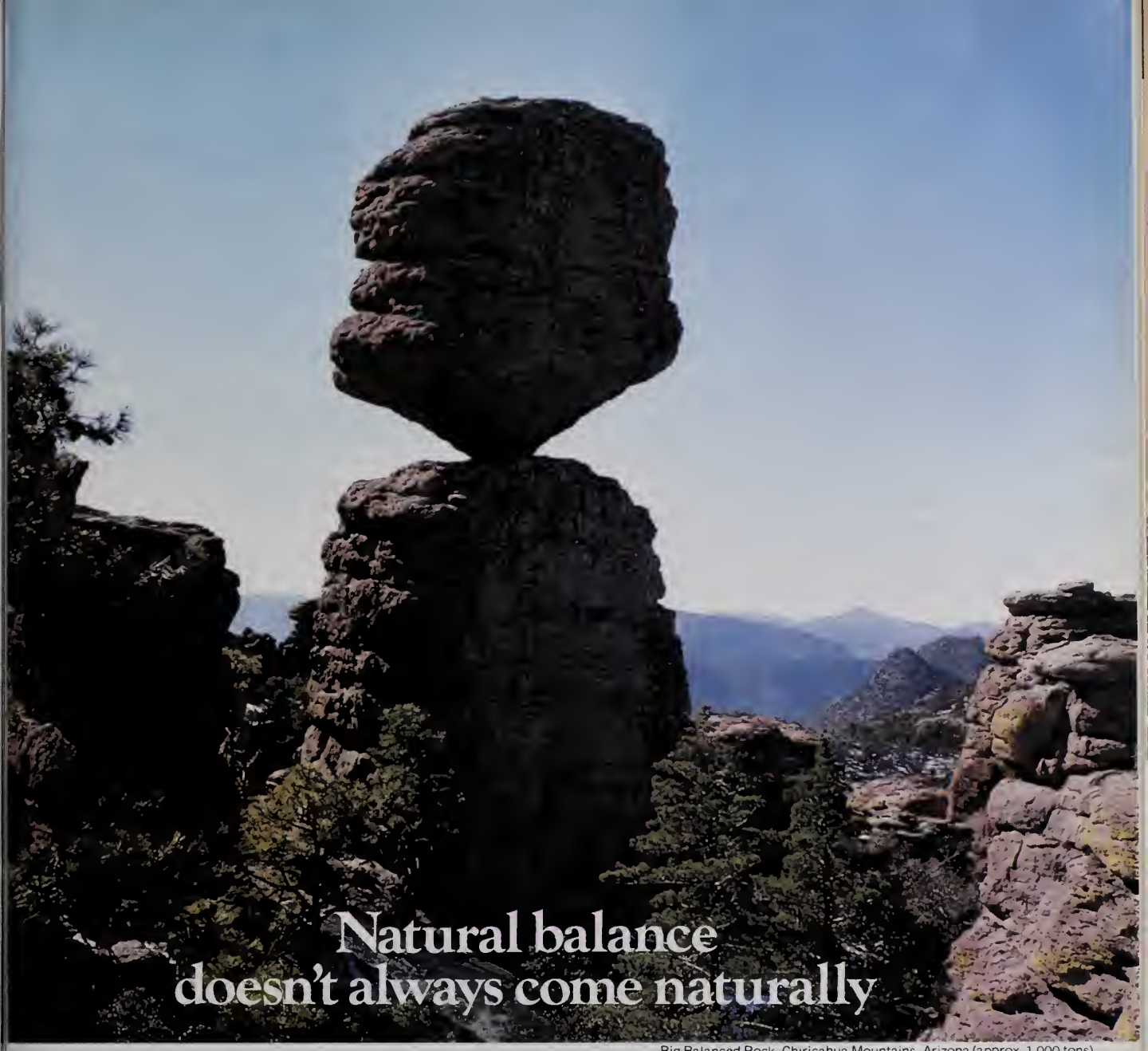
Women in Medicine Scholarship

The Woman's Auxiliary of the Minnesota State Medical Association has been successful in raising funds for the University of Minnesota Medical School. The Ramsey County Auxiliary has asked the Medical School Administration to take affirmative action in support of women in medicine by establishing a tuition scholarship for a female medical student utilizing a portion of the Auxiliary's annual contribution to the Medical School. The scholarship covers full resident tuition for one year, plus University fees.

The Medical School announces the establishment of such a scholarship. It will be known as "The Minnesota State Medical Association's Woman's Auxiliary Scholarship." The Honors and Awards Committee of the Medical School will select the recipient from the applicants. The criteria for selection, as stipulated by the Auxiliary, will be based on scholarship, not on need.

All female medical students are eligible for the award once they have completed Phase A. Applications are due by November 1st, and will be awarded by Winter Quarter. Write to: The Associate Dean for Student Affairs, Box 293, Mayo Memorial Building, Minneapolis, Minnesota 55455.

Janet Harvey Hubbell is a third-year student at the University of Minnesota Medical School with a most distinguished record. She has been unanimously voted the first recipient of the Minnesota State Medical Association Woman's Auxiliary Scholarship for this year.



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tibular system.
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Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy. See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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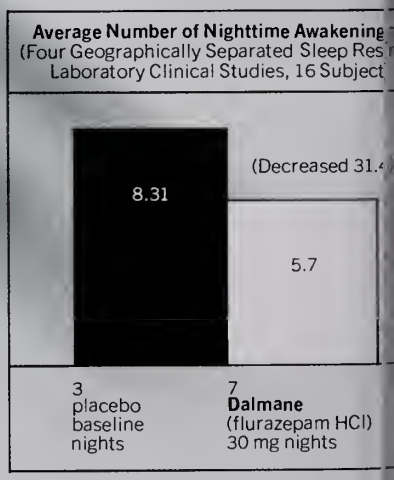
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ERENCES:

racan I, Williams RL, Smith JR: The laboratory in the investigation of sleep leep disturbances. Scientific exhibit at 24th annual meeting of the American hiatric Association, Washington DC, 3-7, 1971

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Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

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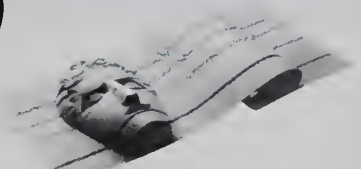
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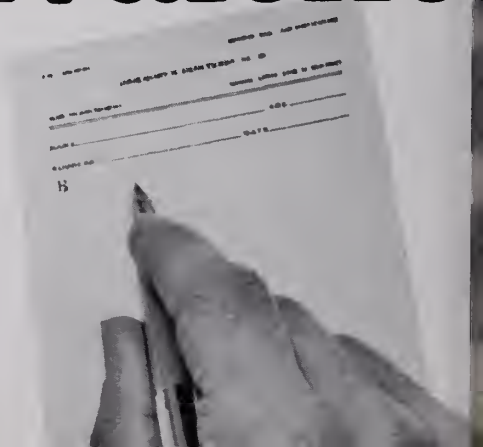
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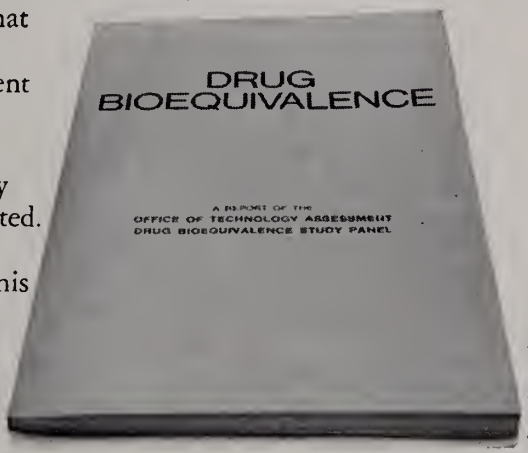
:he weight of scientific opinion:

If the pharmacist substituted a ıemically equivalent drug for the ıe you have specified for your ıtient—could you be certain of that oduct's safety and effectiveness mply because the chemical content as the same?

Definitely not, unless bio-uivalence tests and other quality surance checks had been conducted. he pharmaceutical industry and any scientists have maintained this ɔsition for years, but others have ıestioned it. Now the Office of chnology Assessment of the ɔngress of the United States has ported on the issue in its Drug oequivalence Study.*

Here are a few definitive state-ents in the O.T.A. report:

"...the problem of bioinequiva-ncy in chemically equivalent prod-ts is a real one. Since the studies in ıich lack of bioequivalence was monstrated involved marketed oducts that met current compen-al standards, these documented in-nces constitute unequivocal idence that neither the present ndards for testing the finished oduct nor the specifications for aterials, manufacturing process, d controls are adequate to ensure that ostensibly equivalent drug prod-ucts are, in fact, equivalent in bio-availability.



"While these therapeutic fail-ures resulting from problems of bio-availability were recognized and well documented, it is entirely possi-ble that other therapeutic failures and/or instances of toxicity that had a similar basis have escaped attention."

The Pharmaceutical Manufac-turers Association supports federal legislative amendments that would require manufacturers of duplicate prescription pharmaceutical prod-ucts, subject to new drug procedures, to document:

(a) chemical equivalence; and

(b) biological equivalence, where bioavailability test methods have been validated as a reliable means of assuring clinical equivalence; or

(c) where such validation is not possible, therapeutic equivalence.

In addition, the PMA supports federal legislation that would require certification of all manufacturers of prescription products before they could start in business, annual in-spections and certification thereafter, and strict adherence to FDA regula-tions on good manufacturing practices.

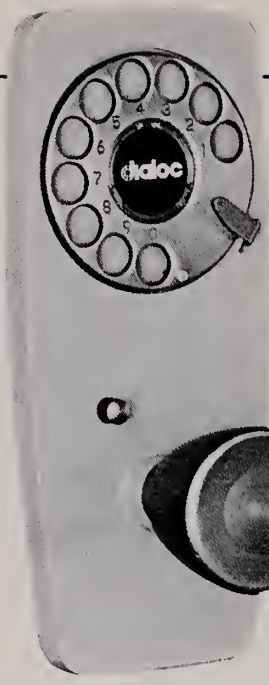
The overall quality of the United States drug supply is excel-lent. But only a total quality assur-ance program, envisaged in these and other policy positions adopted by the PMA Board of Directors in 1974, can bring about acceptable levels of performance by all prescription drug manufacturers and thereby assure the integrity of your prescription...

P·M·A

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*Copies of the complete report on Drug Bioequivalence may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

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Affiliation of the Mayo Foundation with the University of Minnestoa

OWEN H. WANGENSTEEN, M.D.*

DR. WILLIAM WORRALL MAYO came to Minnesota a century and a half (1854) after French explorer Pierre Charles LeSueur's earlier visit to this beautiful and fertile valley. Mayo had come from the Wabash Valley in Indiana to escape recurrent endemics of malaria. There were only 20 physicians in the Minnesota Territory when the Minnesota Medical Society came into being in 1853. Here the elder Mayo saw Indian war at first hand. Minnesota became a state in 1858, and its University acquired its first President, William Watts Folwell, in 1869. Dr. William J. Mayo, the eldest son of Dr. and Mrs. William Worrall Mayo, was born in this house on June 20, 1861, 113 years ago. The house was constructed in 1859 by the deft and practiced hands of his father, aided by his brother, James.

When I went to Europe in 1927-28 to learn something of the methods of European surgeons, Dr. Will Mayo, then a University Regent, volunteered to write letters of recommendation for me. An introduction from the Secretary of State or from the President of the United States could not possibly have served my purposes better. In consequence I was warmly received and treated royally by the top echelon of German professors of surgery, including many inclined after World War I to ignore visiting American surgeons.

When medical men came from Europe to our country as late as the mid 1890's they went usually only as far West as Chicago. However, within a few years thereafter, the fame of the Mayo Brothers, because of their important contributions to greater medicine, complemented by strikingly lower surgical mortalities attending serious operations than could then be achieved by some of the world's finest surgeons, brought medical visitors, especially surgeons, in droves to Rochester, from the Atlantic seaboard of our own country and from Europe and Britain. The visiting surgeons were able to confirm at first hand what they had read in professional journals emanating from the pens of the Mayos. By the end of the first decade of this century, Mayo surgeons had made a unique contribution to surgery's advance.

When George Edgar Vincent, the University's third President, came in 1911, he made out of a number of sleeping, mediocre colleges, a great university through the simple expedient of the power of appointment. A warm mutual understanding grew readily between Vincent and Mayo. An academician like Vincent was probably greatly surprised to find in the practical surgeon a keen interest in and understanding of the importance of higher learning and education for professional men. When Drs. Mayo first came to Vincent with the idea of an affiliation at the Graduate School level between the University and the Mayo Foundation is not precisely known. However, by 1914, Drs. Will and Charles Mayo had agreed to provide the University with an endowment fund in the amount of $1,500,000 to underwrite the cost of graduate training in the medical specialties at Mayos, a fund which in later years grew to $2,000,000.

Guy Stanton Ford, then Dean of the Graduate School, and Dean Elias Potter Lyon of the Medical School staunchly supported the precis of Vincent that such an affiliation become official. The proposition was hotly debated throughout Minnesota, especially by medical faculty members and physicians of both Hennepin and Ramsey Counties. Finally, when legislation was pending to prevent the affiliation between the Mayo Foundation and the University of Minnesota, it was suggested to Dr. Will Mayo that he appear before a meeting of legislators and interested citizens, arranged by the St. Paul Association of Commerce, to present his views. With the eloquence of sincere conviction, Mayo cast his plea in the simplest "neighbor to neighbor" language, using his oft repeated phrase, "My brother and I," and tell-

*Regents' Professor, Department of Surgery, University of Minnesota, Minneapolis.

Presented at the Dedication Ceremonies of the William Worrall Mayo House at LeSueur, Minnesota, Sunday, June 30, 1974.

ing what they hoped to achieve. The winning and persuasive force of Mayo's speech was such that all opposition faded, and the bill to defeat the affiliation died in a legislative committee. Dr. Mayo's presentation has often been alluded to as the Lost Oration.

History does not record a finer and nobler relationship than that which existed between the two brothers, Drs. Will and Charles Mayo. They lived out of the same pocketbook! Those memorable words "my brother and I" were frequently on the lips of each. In tendering the gift to the University, Dr. Will Mayo said, "the peoples' money, of which we have been the moral custodians, is being irrevocably returned to the people from whom it came." Indeed a wonderful philosophy of life!

As late as 1926 at a meeting of the Gridiron Club in Minneapolis at which I was privileged to be present, Dr. Soren P. Rees, a die-hard opponent and a leading physician at the Minneapolis General Hospital, denounced the affiliation in very strong terms. Dr. Will Mayo sitting only a few seats away remarked, "Soren, I have never heard you say it better," an expression that tells a great deal of Will Mayo's ready wit and genius in taking the sting out of vehement opposition.

The affiliation has continued to prosper and today a new Medical School has come into being, utilizing the unusual talents of the Mayo Clinic staff, a school, which in time, undoubtedly will prove to be one of the quality medical schools in our country.

The Mayo Clinic very justly has become an institution of great distinction known throughout the world. From small beginnings here in LeSueur, a truly great medical center has emerged in Rochester under the guidance and aegis of the Mayo Brothers who received their inspiration from their father and mother, with an opportune strong forward thrust from the dedicated and hard working Sisters of St. Francis.

The medical scene today seems a bit confused to most of us and there appears to be a disposition amongst our medical administrators and educators, including representatives of our government, to try to place a physician in every small hamlet throughout our great country. The Mayo Brothers favored the small clinic, staffed with the expertise of specialists, complemented by a few general physicians. I am bold enough to believe that many of you in this audience will live to see the day when Will Mayo's scheme of medical care, provided largely by clinics conveniently located geographically, will get a better hearing to the end that superior medical care will become universally available and at less cost to Society.

It is very fitting indeed that this house, having pleasant memories and important history for this community and Minnesota medicine, has earned the recognition of the Minnesota Historical Society, and received a favorable Nod from its Directors as meriting the place of an early cornerstone in Minnesota medical history.

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Minnesota Medical Foundation

The 13th Annual Distinguished Teaching prizes of the Minnesota Medical Foundation were awarded in October to Drs. Gerhard K. Brand, Jesse E. Edwards and James H. Moller for excellence in teaching University of Minnesota Medical School students. The three teachers were selected for the honor by poll of the medical student body and are the 23rd, 24th and 25th teachers to receive the award since 1962. Each receives a $1,000 prize. Dr. Moller is the first repeat winner of the Distinguished Teaching Award, having also received the award in 1967.

Laboratory Medicine

Practical Virology

Indications and Yield

HENRY H. BALFOUR, JR., M.D.*

Specimens recommended for viral diagnosis according to clinical disease categories are given. Methods of specimen collection and interpretation of results of viral cultures and serologies are provided.

PROBABLY MOST acute infections are caused by viruses. Today's virus laboratory can be useful in making the diagnosis and in managing the patient. The best viral diagnostic results can be expected when the appropriate specimens are obtained and transported properly. Since some antiviral agents are now approved, and many additional antiviral drugs are in the testing stages, tomorrow's virus laboratory will be valuable not only for diagnosis but also for treatment of patients with viral infection.

What to Collect

The specimens of choice for viral isolation according to clinical diagnoses are given in Table 1. Table 2 outlines the methods for specimen collection. I want to emphasize that clinical information is essential to the virologist and hence completion of the requisition cards is most important.

How to Transport It

Ideally, specimens should be transmitted to the virus laboratory within four hours after collection. If this is not possible, material should be stored in a refrigerator, but *not frozen*. No preservatives should be used, and material should be transported to the virus laboratories at approximately 4°C as soon as possible.

Viral Isolation Techniques

The description that follows is applicable to most clinical virology laboratories. Tissue culture is the keystone of viral isolation. Every specimen is inoculated immediately into at least three cell lines. When cytomegalovirus (CMV) is suspected, WI-38 or human foreskin cells are used and when rubella is a consideration, African green

*Director, Division of Clinical Microbiology, Departments of Laboratory Medicine and Pathology, and Pediatrics, University of Minnesota.

Adapted from Laboratory Medicine and Pathology Grand Rounds, January 10, 1975.

TABLE 1
Specimens Recommended for Viral Isolation*

General Disease Category	Specimens Recommended
Neonatal	Throat swab; fresh morning urine; vesicular fluid or swabs if available
Respiratory	Throat swab†
Central Nervous System	Throat swab; stool or rectal swab; urine; CSF; biopsy material; vesicular fluid if available
Gastrointestinal	Throat swab; stool or rectal swab
Exanthems	Throat swab; stool or rectal swab; vesicular fluid if present

*Specimens for viral isolation should be accompanied by an acute serum.

†For respiratory syncytial virus, special arrangements should be made with the virus lab.

TABLE 2
Methods of Specimen Collection for Viral Isolation and Serology

Specimen	Method
Throat swab	Swab posterior pharynx briskly with two sterile dry cotton-tipped applicators. Insert tips of applicators into sterile tube containing media suitable for bacteriologic cultures such as trypticase soy or Hank's balanced salt solution. Culturette tubes are acceptable.
Rectal swab	Insert two cotton-tipped applicators at least 3 cm into rectum. Swab should be stained with stool. Then handle as throat swab.
Vesicular lesions	If vesicles are intact, aspirate at least six lesions with a 25-gauge needle attached to t.b. syringe. Replace hub on needle. Label syringe appropriately and send to lab.
Urine, stool, CSF, biopsy or autopsy specimens	Collect in sterile containers. At least 1 gram of tissue or stool, 2 cc of spinal fluid and 20 cc of urine are adequate.
Serum (for antibody tests)	Two specimens needed. The first as soon after onset of acute illness as possible, and the second two to six weeks later. Collect 7 cc of blood, if possible, in a plain (not anticoagulated) tube. Avoid hemolysis. Do not freeze.

monkey kidney cells or Vero cells are inoculated. Embryonated eggs and suckling mice are available for use in certain circumstances. Cell cultures are examined daily for at least one week. Cultures for CMV are observed for four weeks. Cultures showing cytopathic effect (CPE) are subpassaged and identified by tissue culture neutralization with specific antisera or by immunofluorescence. If specimens do not show CPE, the rhesus monkey kidney tissue cultures are tested for hemadsorption before being considered negative.

Viral Serologic Procedures

Complement fixation (CF) is the method most frequently used in virus laboratories for serologic diagnosis of recent viral infections. The procedure is based on the property of certain antigen-antibody complexes to bind complement (guinea pig serum). Sensitized sheep cells are used as an indicator of complement fixation: these cells hemolyze in the presence of free complement. The CF test is performed in a microtiter system and requires careful control of several variables with overnight fixation at 4°C.

Hemagglutination-inhibition (HI) testing is based on the ability of serum antibodies to inhibit the agglutination of red blood cells (RBCs) by certain viral agents. Rubella immunity is assayed by HI testing using a microtiter system with chick RBCs. Measles (rubeola) immunity is measured by HI testing using African green monkey RBCs.

If a virus is isolated, neutralizing (Nt) titers can be done on paired serum specimens using the patient's own virus. Neutralizing titers are performed by adding virus to serial serum dilutions, incubating the mixtures, and then inoculating them into the appropriate tissue culture system. The Nt titer is expressed as the highest serum dilution that inhibits development of CPE in 50% of the cell cultures.

References will be found on page 429.

Interpretation of Results

How do you interpret a result received from the virus laboratory? Table 3 summarizes the significance of viral isolates according to site of isolation. Isolation of virus from any of the sites in Category 1 is virtually diagnostic of a viral infection *in that area.* For example, isolation of *Herpesvirus hominis* from corneal scrapings is diagnostic of herpes keratitis. Table 4 indicates the significance of viral antibody titers. If the patient's serologic response is a four-fold rise or decline in titer, isolation of the homologous virus from sites in Categories 2 to 4 becomes more significant. For example, if a patient has adenovirus Type 7 isolated from the throat and a four-fold rise in adenovirus CF titer, it is highly probable that the patient's clinical illness is due to adenovirus Type 7.

Limitations of the Virus Laboratory

Without a specific viral isolate, it is impractical to do serologies for coxsackieviruses (29 types including groups A and B) or echoviruses (31 types). In most instances, viral titers on a single serum specimen are meaningless because of heterotypic responses among some viruses and the possibility of persistence of antibody from previous infection.

TABLE 3
Significance of Viral Cultures

Site of Positive Culture	Interpretation
1. CSF, Blood, Biopsy Tissue, Exudates and Transudates, Conjunctival Scrapings, Cervical Swab, Skin Lesions	Virtually Diagnostic
2. Autopsy Material	High Order Association
3. Throat*, Urine*	Moderate Order Association
4. Stool*	Low Order Association

*Move up one category if accompanied by serologic evidence of homologous virus infection.

TABLE 4
Significance of Viral Antibody Titers

Serologic Responses (General)	Interpretation
Four-fold Rise in Titer*	Diagnostic of Recent Infection
Four-fold Decline in Titer*	Diagnostic of Relatively Recent Infection
Single "High" titer or High but Unchanging Titers e.g., CF Titers of 64 to Mumps	Suggestive of Recent Infection
Serologic Responses (Specific Instances)	
Rubella HI Titer $\geqslant 8$	Indicative of Rubella Immunity
Positive Precipitin to La Crosse Virus	Diagnostic of California Encephalitis

*By hemagglutination-inhibition, neutralization, complement fixation or immunofluorescence between acute (collected on or shortly after onset of illness) and convalescent (collected two to six weeks later).

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GROUP OR FAMILY PRACTICE—Over the past 3½ years the Fairmont Medical Clinic has added three new physicians to its staff. At the present time we are actively pursuing one additional man in general or family practice for the summer or fall, 1975. New clinic adjacent to a new 114-bed hospital in a rapidly growing community. Starting salary open, early partnership opportunity. Contact D. E. Grandgenett, Fairmont Medical Clinic. (507) 238-4263.

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STAFF PHYSICIAN—Mankato State College is seeking a staff physician capable of general medicine and committed to working with young adults. Located in south central Minnesota the College has an on-campus enrollment of 9,500 students, and is situated in a metropolitan area of 50,000. Attractive five day work week, vacation when school not in session, position available July 1, 1975. Contact: Karen Delesha, Director, Student Health Service, Mankato State College, Mankato, Minn. 56001. Phone (507) 389-2726.

FAMILY PRACTICE opportunity with multi-specialty clinic. Separate departmental facilities in base community: satellite office in nearby rural community. Unique blending of primary and referral care in same group. Participate in this new approach to rural medicine. Generous starting salary first year incentive thereafter, liberal time off allowance and fringe benefits. Contact D. R. Molesworth, Administrator, Mankato Clinic Ltd., Mankato, Minn. 56001. Call collect 507-387-1811.

RIVERS EDGE MEDICAL CLINIC—Farmington, Mn. needs two additional General Practitioners to practice in a nearly new Clinic, Hospital and Nursing Home. Fast growing area just 45 minutes from St. Paul-Minneapolis. Metropolitan advantage with Community living. Contact M. H. Hunter, M.D. (612) 463-7181.

OFFICE SPACE TO SHARE—Part-time M.D. has space to share in downtown Minneapolis. Receptionist and light bookkeeping provided. In skyway system. Call 339-3095.

(Continued on page 424)

Classified Advertisements

(Continued from page 423)

ONE PICKER 300 M.A. 100 K.V. x-ray machine. Used as straight Radiographic unit. Unit in excellent condition with approximately 3,000 exps. on new x-ray tube. No longer needed by hospital. Very reasonable. Contact Mr. V. T. Graupmann, Business Manager, Anoka State Hospital, Anoka, Minnesota 55303.

PRIVATE PRACTICE OPPORTUNITY—Open your own private practice in a new clinic bldg., now unoccupied 50 miles no. of Mpls. Completely stocked with supplies and equipment for two 3-room doctor suites business office, lab, Xray, emergency, procto etc. rooms, space for three practitioners eventually. Coverage available. Over 25,000 population potential in 15 mile radius, in fast growing area. No investment needed. Free rent. Guaranteed income for first year. Community living with metropolitan advantages. Write Health Manpower Committee, Braham, Minn. 55006 or call 396-2144, L. Schwarten or 396-3633 Dr. Burmaster, area code 612.

GENERAL SURGEON—Twenty-four Man Multi-Specialty Group Practice has immediate need for a third General Surgeon. Prefer Board Certified. Broadly based referral practice in prosperous Southern Minnesota. Excellent Clinic and Hospital facilities. Generous benefit and time off program; excellent starting salary first year; incentive pay plan thereafter. Contact C. H. Brady, M.D. or D. R. Molesworth, Adm., Mankato Clinic, Ltd., Mankato, Minnesota 56001. Call collect 507-387-1811.

WANTED—G.P. for incorporated practice, Lake City, Minnesota. Beautiful new clinic building. New well organized accredited hospital, all air conditioned. Unequaled opportunities for continuing education and professional association. Easy commuting to Rochester and Twin Cities. Beautiful community for family. Excellent schools. On large lake with unparalleled recreational opportunities. Seeking member for full participation. Call Drs. Bowers and Gjerde, P.A. 612-345-3318.

INTERNIST AND PEDIATRICIAN WANTED—Incorporated group of three general surgeons and one obstetrician-gynecologist looking for board qualified or certified internist and pediatrician. We are located in north central Wisconsin serving a community of approximately 25,000 with a summer population of 200,000. We have excellent recreational and educational facilities including college. Anyone interested write to Dr. I. E. Schiek, Jr. or Dr. Otto G. Rosemeyer c/o The Schiek Clinic S.C., Rhinelander, Wisconsin 54501 or call collect 715-362-6160.

FOR SALE—St. Paul Lowry Bldg. Medical Office Practice. Retiring. Well established. Good clientele. Completely equipped. Receptionist here 20 years. Good patient history files. Call (612) 224-2123, (612) 699-4528 (Home).

NEEDED IMMEDIATELY—Two general practitioners to locate in Northwest Iowa, close to Iowa Great Lakes. New medical clinic & very modern hospital serving a large area and very lucrative practice. Excellent financial arrangements. Call or write: Ivan E. Brown, M.D., 551 West Maple Drive, Hartley, Iowa 51346, Phone 712-728-2820 or 712-728-2765.

FOR SALE—NCR 42-28 bookkeeping machine designed for clinical use. Wired to punch paper tape. Master Electric Addresser, and Model C-35 Saxon copier with automatic biller. Call: Ely Medical Center, Ltd. 218-365-3151.

FAMILY PHYSICIAN OPENING—Eight man corporation (5 family practitioners, 1 general surgeon, 2 obstetrician-gynecologists) is seeking a Family Physician. North Minneapolis Metro Area, new modern hospital, rapidly expanding clinic practice, pension and profit sharing, buy-in opportunity, excellent fringe benefits, superb living area. Contact: Matthew Yelle, M.D. or Richard Moore, Administrator, Mork Clinic, P.A., 1833 2nd Avenue South, Anoka, Minnesota 55303, 612-421-3680.

MMI ANNOUNCES STATE-WIDE REGISTRATION. We are presently registering physicians who: (1) Desire coverage for their practice on weekends, or periods of one week to several or more months—OR—(2) Are available to do Locum Tenen on weekends, or periods of one week to several or more months. Write or call M. A. Cornwall, M.D., Medical Director, Midwest Medical, Inc., Lakeland, Minn. 55043—Phone (612) 436-5161.

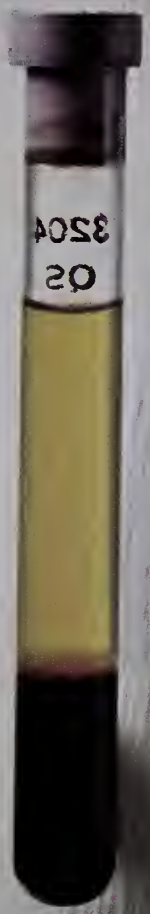
WINONA CLINIC, Winona, Minnesota, is currently searching for one physician in each of the following specialties: OB-GYN, Otolaryngology, Orthopedic Surgery, and Psychiatry. Winona is a picturesque, Mississippi River town. Excellent public and parochial schools and 3 four-year colleges. Compensation in first year, 75% of base salary, second year, 80%; third year, 90%; fourth year, 100%. Other benefits include Disability Insurance, Pension Plan, Profit Sharing Plan, Life Insurance, vacation, time off for meetings, medical society dues and specialty society dues paid, Professional Liability Insurance. Blue Cross-Blue Shield Insurance, medical reimbursement plan, medical books and journals, extended vacation privileges, and a deferred compensation plan. Please write or call, A.E. Edin, M.D., Chairman Recruiting Committee, Winona Clinic, Ltd., 420 E. Sarnia St., Winona, MN 55987 (507) 454-3680.

PHYSICIAN'S ASSISTANT—Seeks employment with solo GP or group practice in larger rural community; soon to complete 2 yr. AMA approved program; vitae, ref., program info. upon request, salary negotiable; interview poss., available May, 1975. Write: Douglas Kaufman, 909 Governeour, #203, Wichita, Kansas 67207.

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- Diet control
- A proven cholesterol-lowering adjunct to diet*
- Convenient once-a-day dosage*
- Reasonable cost*



*Choloxin®
(sodium dextrothyroxine)

agent for low density lipoproteins, "type II hyperlipidemia," in euthyroid, non-cardiac patients.

FLINT LABORATORIES
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Deerfield, Illinois 60015

See reverse side for full prescribing information

Choloxin® (sodium dextrothyroxine)

The Lipid-Lowering Agent with Once-A-Day Dosage

Four strengths . . . 1, 2, 4, and 6 mg. . . . are available making the scored tablet regimen a flexible dosage system. And, for most patients, CHOLOXIN tablets offer once-a-day dosage.

AN IMPORTANT NOTE:
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CHOLOXIN® (sodium dextrothyroxine) Single-Tablet-A-Day Dosage Schedules

See prescribing information in package insert reproduced below.

	Starting Dosage	Increased Monthly by	Usual Maintenance	Maximal Recommended
Adult Hypercholesterolemic	1.0-2.0 mg.	1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac	0.5-1.0 mg	1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as D-3,5,3' 5'-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias, rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

FLINT LABORATORIES
Deerfield, Illinois

Minnesota State Medical Association

Annual Meeting

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MEET

EDUCATE

An Invitation to Educate . . .

Sessions of the House of Delegates

Registration for the House of Delegates will be on Wednesday, May 21 from noon until 1:00 p.m. in the foyer of the Hotel Saint Paul. The two sessions of the House of Delegates, Wednesday, May 21 and Friday, May 23, will convene at 1:00 p.m. in the Ballroom of the Hotel Saint Paul.

Hearing of the Reference Committees

Hearings of the reference committees will convene at 4:00 p.m. Wednesday, May 21 at the St. Paul Hilton Hotel in the following locations:

1. Medical Practice—Pioneer Suite East
2. Medical Economics—Minnesota West Ballroom
3. Medical Organization—Senate Suite
4. Professional Relations—Indian Suite
5. Officers and Councilors—Pioneer Suite West

President's Reception and Annual Banquet

The President's Reception will be held in the Indian Suite of the St. Paul Hilton Hotel at 6:00 p.m. Thursday, May 22. Following the Reception, guests will enjoy dinner, dancing and special entertainment in the Minnesota East Ballroom. The award for the most outstanding scientific exhibit will be presented by the Southern Minnesota Medical Assocation, and the Fifty Club and recipients of special association awards will be honored. Dr. Malcolm Todd, President of the American Medical Association will be among the distinguished guests in attendance.

Bavarian Beer Seminar

This "seminar" invites you to join the camaraderie, enjoy German Bratwurst and music and take home a German stein as a remembrance of this year's Annual Meeting. The fun begins at 3:30 p.m. on Friday at the conclusion of the scientific program (outlined below).

Scientific Program

Total: 14 Credit Hours

General Registration 7:30-5:00 Thursday & Friday

Lobby, St. Paul Hilton

Thursday, May 22, 1975

Seminar—Pioneer Suite: 8:30 a.m.-Noon

"What's New in Dermatology?"

Presented by the Minnesota Dermatological Society

8:30 a.m.—Drug Reactions

What's New in Therapy?

Cutaneous Signs of Systemic Disease

Today's Scabies

10:30 a.m.—Malignant Melonoma

Panel Discussion on Diagnosis and Therapy

Thursday, May 22, 1975

Seminar—Senate Suite—8:30 a.m.-Noon

Part I—Diagnosis & Management of an Acutely Painful Joint

Part II Prognosis & Management of Various, Specific Orthopaedic Problems

Presented by the Minnesota State Orthopaedic Society

8:30 a.m.—*The Management of the Acutely Painful Joint*

History, examination, differential diagnosis, laboratory examination and procedures to help establish diagnosis, emergency management, long term management.

Presentation of Specific Problems

Non Traumatic Mono-Articular Synovitis

Septic Joint

Gonococcal Arthritis

Traumatic Knee Joint with Fracture

Knee Joint with Ligamentous Instability

Knee Joint without Ligamentous Instability

Intervertebral Disk Space Infection

10:30 a.m. *Specific Orthopaedic and Fracture Problems (con't.)*

Management of Pelvic Fractures

Tennis Elbow

Management of Closed Infected Hand

Management of Common Fractures of the Hand

Diagnosis and Management of Complications Following Cast Application

a. Common Peroneal Nerve Palsy
b. Compartment Syndrome
c. Too loose or too tight cast

Finger-tip Injuries
Puncture Wound of the Foot
Round Table Discussion: Questions and Answers

Thursday, May 22, 1975

Seminar—Indian Suite—8:30 a.m.-Noon

Respiratory Problems
Presented by Minnesota Thoracic Society and the Minnesota Chapter, American College of Chest Physicians

8:30 a.m.—Panel—Current Concepts in Adult Respiratory Distress Syndrome (Shock Lung)
Clinical Presentation of Adult Respiratory Distress Syndrome
Pathophysiological Mechanisms in Adult Respiratory Distress Syndrome
Therapeutic Considerations in Adult Respiratory Distress Syndrome with Emphasis on the use of P.E.E.P. (Positive End Expiratory Pressure)

10:15 a.m.—Panel: Current Concepts in Therapy of Respiratory Disease
The Value and Role of New Antibiotics in the Treatment of Pulmonary Infections
The Use of Corticosteroids in the Treatment of Pulmonary Disease
Chemoprophylaxis in Tuberculosis. When to Treat a Positive P.P.D.

Thursday, May 22, 1975

General Session—Minnesota West Ballroom—8:30 a.m.-Noon

Surgical Infections—A Panel Discussion
Presented by the Minnesota Chapter of the American College of Surgeons

8:30 a.m.—*The Prophylaxis of Surgical Infections*
Prophylactic Antibiotics in Human Bites of the Hand
Use of Antibiotics in the Treatment of Burns
Prophylactic Antibiotics in Vaginal Hysterectomy
Preparation of the Bowel for Colon Surgery
Prevention of Infections Following Urethral Instrumentation

10:30 a.m.—*Treatment of Surgical Infections*
How to Obtain Material for Culture
Antibiotics for Anaerobic Infections of the Abdomen
Chronic Infections of the Urinary Tract
Gram Negative Bacteremia
The Contaminated Abdominal Wound
Postoperative Pulmonary Infections
Questions and Discussion with Audience Participation

Thursday, May 22, 1975

Luncheon Speaker: William A. Nolen, M.D., surgeon, Litchfield, Minnesota
Author—"The Making of a Surgeon," "A Surgeon's World," "Healing: A Doctor in Search of a Miracle."
Topic: Doctor-Patient Communication Gap.

Thursday, May 22, 1975

Seminar—Pioneer Suite—1:30 p.m.—5:00 p.m.

Continuing Education in Ophthalmology
Presented by the Minnesota Academy of Ophthalmology and Otolaryngology
Differential diagnosis of the Red Eye
Retinal signs of Systemic Disease
Detection of Glaucoma

Thursday, May 22, 1975

Seminar—Senate Suite—1:30 p.m.—5:00 p.m.

The Physician and the Government—A Panel Discussion presented by The Minnesota Component of the American Society of Internal Medicine
3:30 p.m.—Continuation of Panel Discussion

Thursday, May 22, 1975

Seminar—Indian Suite—1:30 p.m.-5:00 p.m.

Infectious Disease
Presented by Department of Medicine, Section of Infectious Disease, Hennepin County Medical Center

1:30 p.m.-3:00 p.m.—
Bacterial Meningitis
Bacterial Pneumonias
Gonococcal Infections
Urinary Tract Infections

3:30 p.m.-5:00 p.m.—
Use of Aminoglycoside Antibiotics
Infectious Adenopathy
Newer Penicillins and Cephalosporins
Work Up of Patients with Recurrent Infections
Rabies

Thursday, May 22, 1975

General Session—Minnesota West Ballroom—1:30 p.m.-5:00 p.m.

Immunology and Allergy
Presented by the Minnesota Allergy Society

1:30 p.m.—New Immunological Advances in the Pathogenic Mechanisms in Bronchial Asthma
Diagnostic Tests in Allergy
Clinical Application of the RAST Test in Allergy

3:45 p.m.—New Advances in the Management of Bronchial Asthma
Management of Bronchial Asthma—Panel Discussion with Audience Input

Friday, May 23, 1975

General Session—Minnesota West Ballroom—8:30 a.m.-10:00 a.m.

Treatment of Rheumatoid Arthritis—The Old and the New
Presented by the Committee on Rheumatic Diseases of the Minnesota State Medical Association

8:30 a.m.—Use of the Basic Program, Antimalarials and Gold Therapy in the Treatment of Rheumatoid Arthritis
New Drugs and Indications for the Use of Immunosuppressives in the Treatment of Rheumatoid Arthritis
Indications For and Results Of Total Joint Replacement in Rheumatoid Arthritis

Friday, May 23, 1975

Seminar—Indian Suite—8:30 a.m.-Noon

Symposium—Inflammatory Bowel Disease
Presented by the Minnesota State Medical Association

8:30 a.m.—Anal Manifestations of Inflammatory Bowel Disease
Differential Diagnosis and Management of Inflammatory Bowel Disease
Ulcerative Proctitis
Toxic Megacolon
Indications for and Results of Surgery for Inflamma-

tory Bowel Disease
Discussion

10:30 a.m.—Symposium—Management of Common Anorectal Disorders
Anorectal Emergencies: Abscess, Thrombosed Hemorrhoid, Acute Fissure, and Rectal Prolapse
Condylomata Acuminata
Hemorrhoids and Fistula-in-ano
Pruritus Ani
Pilonidal Disease
Discussion

Friday, May 23, 1975

Seminar—Senate Suite—8:30 a.m.-Noon
Colon and Rectum Cancer: Early Diagnosis, Prevention and Modern Day Treatment
Presented by the Minnesota Division, American Cancer Society
Early Diagnosis and Prevention

8:30 a.m.—Proctosigmoidoscopy in Prevention of Bowel Cancer
Diagnostic Colonoscopy
Colonoscopy and Polypectomy
Immunodiagnosis
Cancer Syndromes
Questions and Discussion with Audience Participation.
Modern Day Treatment

10:30 a.m.—Local Treatment
Pre-Operative Radiation
Choice of Surgery for Rectal Cancer
Chemotherapy
Hepatic Artery Infusion
Questions and Discussion with Audience Participation.

Friday, May 23, 1975

Seminar—Pioneer Suite—8:30 a.m.-5:00 p.m.
Human Sexuality in Clinical Practice
Presented by the University of Minnesota Medical School Program in Human Sexuality
An intensive six hour seminar limited to 40 participants, it will focus upon human sexuality and its relationship to medical practice. The format will consist of small group discussions, stimulated by film portrayal of a wide range of sexual behavior, and presentation of up-to-date and accurate information regarding sexual behavior.
Topics to be covered will include self eroticism, sexual relationships, common sexual problems, therapeutic techniques and sex and aging.

Friday, May 23, 1975

General Session—Minnesota West Ballroom—10:30 a.m.-Noon
Chronic Pain: Genesis and Early Management
Presented by the Minnesota State Medical Association

10:30 a.m.—A Panel Discussion
Drawing on the experience of four doctors with diverse approaches to the treatment of patients with pain, the panel will discuss the factors that contribute to the development of a chronically painful condition. Particular attention will be paid to the role of the medical profession in the development and the early management of pain. Psychologic factors, home and family relationships, drug therapy and abuse, iatrogenic disease and the new theories of pain physiology will be presented. Finally, a variety of specific therapies currently available or under investigation will be described.

Friday, May 23, 1975

12:15 Luncheon—Speaker: Elisabeth Kubler-Ross, M.D., Physician and Psychiatrist, Flossmoor, Illinois
Author: "On Death and Dying" and "Questions and Answers on Death and Dying."
Program Topic—Death and Dying

Friday, May 23, 1975

General Session: Minnesota West Ballroom—1:30 p.m.-3:00 p.m.
Death and Dying (Emotional Needs of the Dying Patient and the Family)
Presented by the Minnesota State Medical Association
Adjustment to terminal illness including "Shapes of Dying" and the symbolic language of terminally ill patients will be discussed with special reference to dying children and the issue of prolongation of life.

References

Practical Virology—Balfour, Jr. (page 422)

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4. Hanshaw JB: Cytomegalovirus infection and cerebral dysfunction. Hospital Practice 5:111, 1970.
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Disruptive anxiety usually meets its match here.

• Often effective when reassurance and counseling are insufficient.
• Three dosage strengths to meet most therapeutic needs.

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.

Contraindications: Patients with known hypersensitivity to the drug.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (e.g., operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation, or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions:

ORAL: In the elderly and debilitated and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six.

INJECTABLE: Keep patients under observation, preferably in bed, up to three hours after initial injection; forbid ambulatory patients to operate vehicle following injection; do not administer to patients in shock or comatose states; use reduced dosage (usually 25 to 50 mg) for the elderly or debilitated and for children age twelve or older.

ORAL AND INJECTABLE: Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating compounds such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (e.g., excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual



precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

With the injectable form, isolated instances of hypotension, tachycardia and blurred vision have been reported; also hypotension associated with spinal anesthesia, and pain following I.M. injection.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral: Adults:* Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)

For Parenteral Administration: Should be individualized according to diagnosis and response. While 300 mg may be given during a 6-hour period, do not exceed this dose in any 24-hour period. To control acute conditions rapidly, the usual initial adult dose is 50 to 100 mg I.M. or I.V. Subsequent treatment, if necessary, may be given orally. (See Precautions.)

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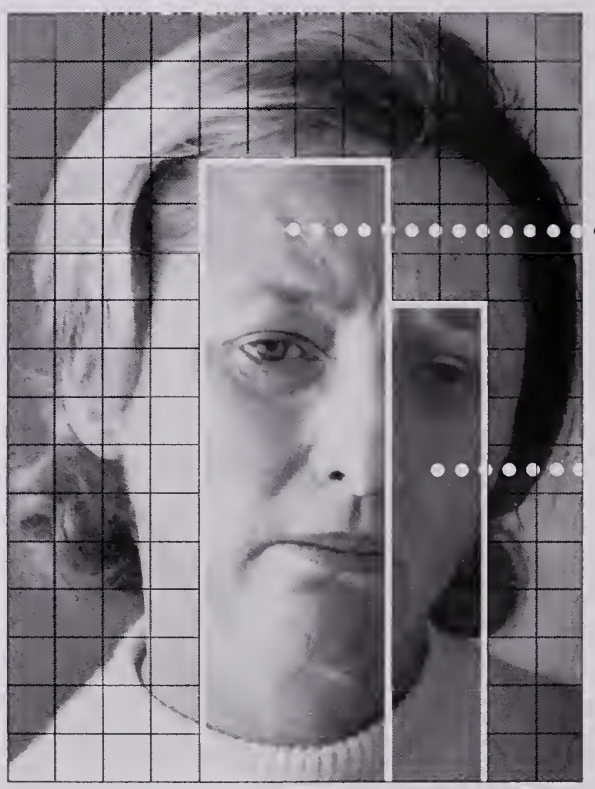
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Reuben Berman, M.D.

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JUNE 1975

Both often



Predominant psychoneurotic anxiety

Associated depressive symptoms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequen and/or severity of grand mal seizures n require increased dosage of standard a convulsant medication; abrupt withdra may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous i gestion of alcohol and other CNS depre sants. Withdrawal symptoms (similar t those with barbiturates and alcohol) ha occurred following abrupt discontinuar (convulsions, tremor, abdominal and m cle cramps, vomiting and sweating). Ke addiction-prone individuals under care

respond to one

According to her major
mptoms, she is a psychoneu-
tic patient with severe
nxiety. But according to the
escription she gives of her
elings, part of the problem
ay sound like depression.
his is because her problem,
though primarily one of ex-
ssive anxiety, is often accom-
anied by depressive symptom-
ology. Valium (diazepam)
n provide relief for both—as
e excessive anxiety is re-
ved, the depressive symp-
ms associated with it are also
ten relieved.

There are other advan-
ges in using Valium for the
anagement of psychoneu-
tic anxiety with secondary
pressive symptoms: the
ychotherapeutic effect of
alium is pronounced and
pid. This means that im-
ovement is usually apparent
in the patient within a few days rather than in a week or two, although it may take longer in some patients. In addition, Valium (diazepam) is generally well tolerated; as with most CNS-acting agents, caution patients against hazardous occupations requiring complete mental alertness.

Also, because the psychoneurotic patient's symptoms are often intensified at bedtime, Valium can offer an additional benefit. An *h.s.* dose added to the *b.i.d.* or *t.i.d.* treatment regimen can relieve the excessive anxiety and associated depressive symptoms and thus encourage a more restful night's sleep.



Valium® (diazepam)

2-mg, 5-mg, 10-mg tablets

in psychoneurotic
anxiety states
with associated
depressive symptoms

urveillance because of their predisposi-
on to habituation and dependence. In
regnancy, lactation or women of child-
earing age, weigh potential benefit
gainst possible hazard.

recautions: If combined with other psy-
hotropics or anticonvulsants, consider
arefully pharmacology of agents em-
loyed; drugs such as phenothiazines,
arcotics, barbiturates, MAO inhibitors
nd other antidepressants may potentiate
s action. Usual precautions indicated in
atients severely depressed, or with latent
epression, or with suicidal tendencies.
Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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another type for TYLENOL® acetaminophen product



When the post-T & A patient requires an analgesic, a new problem arises. Hemorrhagic tendencies following the use of aspirin after tonsillectomies have been reported.[1,2] In a patient who "...has recently undergone a surgical procedure or has another underlying hemostatic defect, aspirin ingestion may cause significant bleeding....Aspirin is absolutely contraindicated in such situations. Acetaminophen...could replace aspirin in these instances."[3]

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References: 1. Reuter, S.H., and Montgomery, W.W.: Arch. Otolaryng. *80*:214-217 (Aug.) 1964. **2.** Osol, A., et al., ed.: The United States Dispensatory and Physicians' Pharmacology, ed. 26, Philadelphia, J.B. Lippincott Co., 1967, p. 171. **3.** Schwartz, A.D., and Pearson, H.A.: J. Pediat. *78*:558-560 (March) 1971.

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President's Letter



A Tribute to Barney

THE PRESIDENT'S Letter in MINNESOTA MEDICINE offers the President of the Minnesota State Medical Association a unique opportunity to communicate with the members. It can be and has been used in many ways—to discuss current issues and problems, to sell an idea, to philosophize, to get the input of other medical leaders and to exert leadership. There always has been something of a problem with the first letter as it is written in April almost a month before the writer assumes the office and almost two months before publication. Fortunately, this was not a problem this year as I have a message that should be presented now—a special tribute to Barney Hall, our immediate Past President.

All the cliches, such as he is a hard act to follow or his shoes will be hard to fill, have been applied to Barney and his presidency. It would seem more appropriate, however, to salute him and record our heartfelt thanks for the excellent job he did in behalf of all of us.

Barney carried out the double duties of President of the Association so well, providing strong effective leadership and performing ceremonial duties in a friendly, dignified manner.

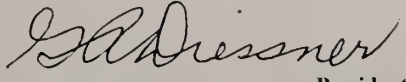
No President served more conscientiously. His dedication to the office was complete. When his assistance was asked, no problem was too minor and no meeting too insignificant to attend. He spent an unbelievable amount of his time during the past year on Association activities, mainly by sacrificing the time he might have spent with his colleagues, his patients, and his family.

No President served more patiently in the Association's negotiations and encounters with bureaucracy and governmental agencies. Barney is known and respected by leaders in the state legislature and in business organizations who share our concerns and interests.

No President served with more wisdom and dignity. His honest, friendly, open personality has been refreshing in these times when leaders are suspect and often accused of deceit, deviousness, hostility, and unavailability.

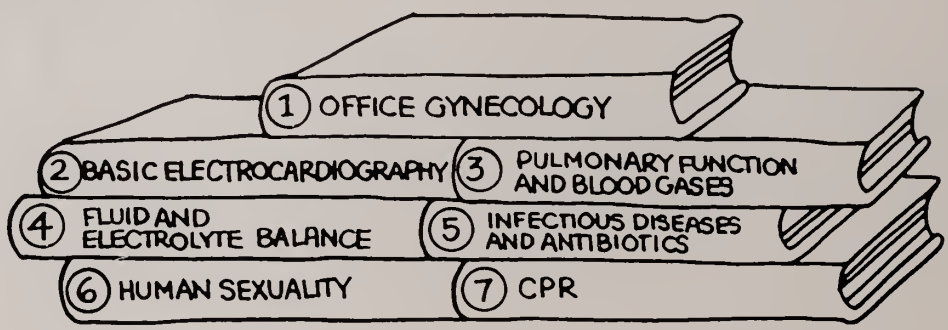
Although presidency of the Association was a high point of his service to the State Medical Association, he served effectively in many important posts in the organization including: Secretary, Councilor from the Fifth District, and Chairman of the Finance Committee. May his record and accomplishments be an inspiration for our members to give a measure of his dedicated service.

Dr. Barnard Hall, we salute you.



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*Courses 1 through 5 are 6 hours each; each is presented twice (once on Saturday, once on Sunday); and each costs $70. Courses 6 and 7 are 12-hour courses that run both days and their costs depend on package options elected by registrants.

For more information, **WRITE:**
Dept. of Circulation & Records/AMA, 535 N. Dearborn St./Chicago, IL 60610
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Editor's Notebook

On Shortening Manuscripts

I have been on this job for six months, and I've read about one hundred manuscripts. Many are excellent, but many are too long.

Why is this? Medical authors are not inherently long-winded. Nor do they necessarily want to puff up their ideas. Their reasons for longness are far simpler than that. They simply want to be *objective, scientific,* and *self-effacing.* These are the noble ideals of the medical profession, but they may result in wordy prose because of excess caution. Below are examples of wordiness cited in the *Council of Biological Editor's Style Manual!*[1]

Wordy	Concise
The quantitative findings reported by Smith were analyzed and seemed, according to our interpretation, to contain significant inconsistencies. Our reasons for attaining this diverse opinion are . . .	We question Smith's measurements because . . .
A method, which was found to be expedient and not very difficult to accomplish and which possessed a high degree of accuracy in its results, was devised whereby . . .	I devised a simple, accurate method to . . .
One might well be censured for so tenaciously propounding this hypothesis in view of the weight of evidence to the contrary.	I was wrong.
if conditions are such that	if
in all cases	always, invariably
in order to	to
in terms of	in
in the event that	if
in view of the fact that	since, because
it is often the case that	often
it is possible that the cause is	the cause may be
it is this that	this
it would thus appear that	apparently
Concerning this matter it may be borne in mind that In this connection the statement may be made that It is interesting to note that It has long been known that It may be said that Typical results are shown With respect to the occurrence of these types, it has been found that	Omit such introductory phrases.

How else can you cut the length of your medical prose? I don't know all the answers, but I use these rules of thumb for my own work. You may find they will help you shorten your manuscripts:

1. Get to the point of the paper immediately, preferably in the first sentence,

definitely in the first paragraph. If you're going to hit a nail, hit it on the head.

2. Reconsider the way your paper is organized. If you can't capture the essence of it in a single paragraph, your subject matter is probably either too broad or you haven't organized it properly. I like to arrange my ideas in the form of a critical argument. The natural arrangement is:[2]

> Statement of problem.
> Marshalling of evidence, first on main points, then on subsidiary ones—the same sequence kept throughout the argument.
> Credibility of evidence examined.
> Statement of possible implications of all evidence not wholly rejected.
> The weighing of conflicting evidence in the scale of probability.
> Verdict.

3. Calculate the average number of words per sentence. Ideally the average ought not to exceed 15. If your average number exceeds 20 or 25, shorten your sentences.
4. Write with verbs, not nouns. To spot overuse of nouns, look for nouns ending in *-ion*. In most cases, you can change those nouns into verbs, e.g. *describe* rather than *description*. Below I show how this change cuts sentence length.

Before Revision	After Revision
Then the *decision* was arrived at that an *exploration* of the other possibility was deemed advisable. (16 words).	Then we *decided* to *explore* the other *possibility*. (eight words, 100% decrease)
We then made an *investigation* of what the *causes* were for the *mutation* of the cells. (16 words)	We *investigated* what *causes* cells to *mutate*. (seven words, 130% decrease)
The best means for the *enlargement* of the cavity by surgeons is by means of a lateral *incision*. (18 words)	Surgeons *enlarge* the cavity by *incising laterally*. (seven words, 160% decrease)

5. Be on the lookout for *by, which,* and *of*. Frequent use of these words usually are signs of wordiness: (1) *by* because it often means a sentence is written in the passive voice; (2) *which* and *of* because they often are a sign of "by and which disease." This disease is a form of intellectual laziness that leads to sentences like this:[1]

> Many biological journals, especially those *which* regularly publish new scientific names, now state in each issue the exact date *of* publication *of* the preceding issue. In dealing with journals *which* do not follow this practice, or with volumes *which* are issued individually, the biologist often needs to resort to indexes . . . in order to determine the actual date *of* publication *of* a particular name.

6. When it is possible to cut a word out, a sentence out, or a paragraph out, cut it out.
7. Have something to say, say it, and stop when you've said it.
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Richard L Reece MD

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Opacification of the "Para-Lymphatic System" during Lymphography*

HANS KUISK, M.D., D.Sc.,† TIMOTHY E. TULLY, M.D.‡ and ERLING A. KLOPPEDAL, M.D.‡

Lymphography may show tubular structures when lymphatics are obstructed. These structures may resemble vascular structures or nerve bundles. Actually contrast material probably fills perivascular or perineural spaces to produce this appearance. This report contains lymphographs of these structures in a 50-year old male who had lymphatic obstruction from regional node dissection for carcinoma of the penis.

IN THE PRESENCE OF lymphatic obstruction, tubular appearing structures may become opacified during lymphography. They may resemble a vascular tree or a nerve trunk,[3,4,10] and may present a picture that is quite puzzling to the novice lymphographer. According to Wallace,[9] this appearance is produced by contrast material. filling the nonendothelialized perivascular or perineural spaces which communicate with the lymphatic system, thus forming an auxiliary pathway, the para-lymphatic system (PLS).

Case Report

The patient is a 50-year-old male with squamous cell carcinoma of the penis. His penis was amputated, followed by regional lymphadenectomy. No radiotherapy was used. When tumor recurred, the patient was placed on chemotherapy. At the time of pedal lymphography the patient had edema in the lower extremities.

Figure 1 presents the lymphangiographic view at the end of Ethiodol injection. Branching tubular structures are outlined among the extravasated flakes of contrast medium. Instead of normal, straight lymphatic trunks, an almost reticulated appearance of the collateral lymphatics, reaching toward the skin surface is present. This is indicative of an obstruction located proximally.

The 24-hour follow-up roentgenogram (Figure 2) shows further delineation of these ramifying tubular structures. The collateral lymphatic network has lost



Fig. 1—Initial lymphographic appearance of the leg in secondary lymphedema, caused by lymphatic obstruction at the inguinoiliac level due to post-operative recurrence of metastatic carcinoma of the penis.

*From the Departments of Radiology, University of Minnesota and Veterans Administration Hospital, Minneapolis.

†Associate Professor, Department of Therapeutic Radiology, University of Minnesota, Chief, Therapeutic Radiology Service, Veterans Administration Hospital, Minneapolis.

‡Fellow, Diagnostic Radiology Service, University of Minnesota and Veterans Administration Hospital, Minneapolis.

‡Assistant Professor, Department of Diagnostic Radiology, University of Minnesota, Staff Radiologist, Diagnostic Radiology Service, Veterans Administration Hospital, Minneapolis.

most of its contrast medium, but some of the retained oil is still noticeable in the larger lymphatics. Pelvic views reveal a large area devoid of contrast medium extending from the inguinal level upward. This was due to previous surgery and recurrence of the tumor which produced severe obstruction to the lymph flow.

A venogram (Figure 3) clearly identifies the tubular structures as veins and rules out any concomitant venous obstruction. A follow-up roentgenogram (Figure 4) taken about five months after the pedal lymphography shows the veins still opacified although with considerable loss of retained Ethiodol. There is also reduction of previously noted extravasated contrast medium.

Discussion

The pictures presented above show the typical opacification of the perivenous portion of the so-called "para-lymphatic system" (PLS). This term was introduced by Wallace who derived it from a concept of Ottaviani.[9-11] According to the concept, PLS is represented by nonendothelialized spaces, clefts and channels which surround vessels, and nerves, and are also present in perialveolar septa of the lung, as well as less defined areas of the viscera, bones and brain. Such a system would become important in lymphatic obstruction due to its communication with the endothelialized lymphatic channels. It would provide an auxiliary system, helpful in relieving the lymphatic pressure.

Herman et al.[4] have reported perivascular lymphangiographic opacification in an edematous upper extremity of a breast cancer patient who had a history of previous mastectomy and irradiation. Such opacifications are difficult to differentiate from extravasation as both occur commonly together.[2,7]

The concept of the functioning PLS has its supporters.[1,5,8] Ishida et al.[5] reported venous type of PLS opacification in ten extremities of nine patients out of 450 with lymphographs. They were patients with carcinomatous and inflammatory involvement causing lymphatic obstruction; five of the patients had previous surgical intervention. These authors noticed that the initial arborizing pattern increased in density over a period of three days, and then showed a decrease



Fig. 2—Twenty-four hour follow-up view showing clearly the opacified tubular structures, retained contrast medium in the lymphatics, and flaky appearance of the extravasated medium.



Fig. 3—The venogram of the leg following the lymphographic study. It rules out any co-existing venous obstruction and verifies the venous nature of the opacified tubular structures.

30 days later. Venography verified that the opacifications had occurred around the veins. These authors also obtained similar appearances experimentally in dogs. They produced lymphatic obstruction by inducing inflammation prior to lymphography.

Temmer and Sipus[8] described a newborn male with lymphedema of the lower extremities. After finding no lymphatics they could cannulate, they injected three ml of Lipidol Ultra-fluid into the interstitial tissues of the dorsum of the foot. This brought out a striking outline of a widely arborizing tubular structure, identified by venography as a vein. They concluded that PLS was the only functional pathway available for the lymphatic flow. Kinmonth[6] believes that an injection of contrast oil alongside a small vein will produce cephalad progression of oil in the perivenous areolar tissue. This could certainly account for the striking lymphographic appearance in Temmer's patient.

On the other hand, the present authors have observed cases where the lymphatic trunks opacified before the perivenous opacification.[7] This occurred in the case illustrated here. The authors believe that the mechanism is as follows: the contrast medium under high pressure in the lymphatic trunks may enter, in retrograde fashion, a small lymphatic which drains the adventitia of the vein and its tributaries through the cleavage which starts at the rupture site, thus opacifying the periphery of the vein, sometimes for a considerable length.

True periarterial and perineural opacifications have not been demonstrated so far. The persistent retention of contrast media in the perivenous tissue speaks against the concept of a functioning PLS, but this is open to further investigation.



Fig. 4—(Courtesy of Dr. Henry J. Krawcvyk, Fargo, North Dakota). Follow-up roentgenogram about five months after the pedal lymphography. The retention of iodized oil in the PLS is still present, although in decreased amounts, as is the extravasated oil.

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Factors Determining Early Kidney Function

Following Clinical Preservation

LUIS H. TOLEDO-PEREYRA, M.D.;* ALLEN W. MOBERG, M.D.;*
CLIVE O. CALLENDER, M.D.;* RICHARD L. SIMMONS, M.D.*
and JOHN S. NAJARIAN, M.D.

One hundred and eighteen cadaver kidneys were preserved by hypothermic pulsatile perfusion at the University of Minnesota. Eighteen percent of these kidneys were eliminated for transplantation mainly because nonavailable recipients and warm ischemic damage. Of eighty-four kidneys transplanted at this medical center, sixty-eight percent functioned immediately upon grafting, thirty-one percent had a delayed function and one percent never functioned. Prolonged preservation and warm ischemic damage were the most important nonimmunological factors that adversely affected the early kidney function after grafting.

BETTER RESULTS in cadaveric renal transplantation are due to improved immunosuppressive therapy, better histocompatibility testing, and reliable organ preservation techniques. The presence of warm ischemia and the prolonged preservation time before grafting are still the two most important nonimmunological factors in determining an immediate renal function postgrafting.[2,3,5] We have examined these preservation factors that might influence the immediate outcome of the transplanted kidneys.

Materials and Methods

Within 23 months, 118 potential kidney grafts were obtained from 59 cadaver donors, (two to 53 years old) with irreversible brain damage as a result of accident (70%) or natural disease (30%) (Table 1). Normal urinalysis, blood urea nitrogen, creatinine, electrolytes, blood sugar, two hour creatinine clearance and a normal history, were considered in the final evaluation. Adequate levels of fluids were administered to maintain stable central venous pressure and urinary output before surgery. Bilateral nephrectomies were performed by the Donor Team. During the operative procedure, most of the donor patients received furosemide (0.5-2.0 mg/kg), methylprednisolone (30 mg/kg), and in some cases phenoxibenzamine (1 mg/kg). Some donor patients also received 20 mg/kg of antilymphocyte globulin (ALG). After nephrectomy, the kidneys were flushed with 4° Ringer's lactate with heparin (10,000 U/L) and procaine (1 gm/L), until the venous effluent was clear. Immediately thereafter, the kidneys were placed in the Minnesota Mox-100 perfusion system[8] at a systolic perfusion pressure of 60 mmHg, PO_2 200 mmHg, osmolarity 280 mOsm, pH 7.4, temperature 7°C. Cryoprecipitated plasma (CPP) was used as the regular perfusate,[1] except in three kidneys which were perfused with salt poor albumin (Cutter Laboratories). Regular additives were added to both perfusates before use.[1,8]

The perfusate pressure, perfusion flow, blood gases, electrolytes and lactic acid dehydrogenase (LDH) were determined every four hours. All kidneys with a flow of less than 1.0 ml/ min/gm, high perfusion pressure, high levels of LDH, and/

TABLE 1
Causes of Donor Death

Accidental	**70%**
Traumatic Head Injury	34
Suicide/Drug overdose	4
Carbon Monoxide	1
Suffication	1
Natural Diseases	**30%**
Cerebral Vascular Accident	12
Brain Tumor	4
Other	3

*Department of Surgery, University of Minnesota Health Sciences Center, Minneapolis, Minnesota.
Supported by USPHS Grant 5-PO2-AM13083.
Address reprint requests to Dr. Toledo-Pereyra, Box 223, Department of Surgery, Mayo Memorial Building, University of Minnesota, Minneapolis, Minnesota 55455.
See editorial, page 467.

or severe vascular abnormalities were eliminated for transplantation. If the kidney had to be transported to another transplant center it was kept in the transport module until delivered. In some instances, the kidneys were kept at 0°−4°C for several hours before transplantation.

The time that elapsed from the clamping of the renal artery (or absent blood pressure in the donor) until the kidney was first immersed in ice saline was recorded as the "warm ischemia" time. The period of kidney immersion in ice saline until the moment of revascularization in the recipient was recorded as the "cold ischemia" time. The histocompatibility testing was performed on peripheral blood donor lymphocytes or lymph nodes removed at the time of the nephrectomy, and the recipients were selected on the basis of histocompatibility matching. Transplantation of the cadaver donor kidneys was performed by standard techniques, and a postoperative function was followed by daily measurements of urine output and serum creatinine. A diagnosis of rejection was based on otherwise unexplained deterioration in renal function and the appearances of the renal biopsies.

Results

Ninety-seven (82%) of the potential kidneys were transplanted. Table 2 lists the reasons for not using the remaining 21 (18%) kidneys. Thirteen kidneys were sent to other institutions, and 84 were transplanted in 77 patients at this University. The average preservation time for those grafted here was 19.8 hours. Twenty-three patients developed acute tubular necrosis (ATN) after transplantation and required one to five weeks of hemodialysis (Table 3). Sixteen of these patients had functioning kidneys, one kidney never functioned secondary to cortical necrosis, three patients died of sepsis with good kidney function, one patient's kidney had good function, but the kidney was lost due to ureteral leakage; although function returned in two other kidneys rejection followed.

TABLE 2
Kidney Utilization
(May '71-March '73

118 Cadaver Kidneys (59 donors)			
Transplanted:			**97 (82%)**
Perfused		95	
Not used:			**21 (18%)**
No recipient		8 (7%)	
Triple artery		2	
Perfusion failure		2	
Technical error		3	
Polar vessel	(2)		
Ureteral damage	(1)		
Warm ischemia (poor flow)		6	

TABLE 3
Duration of Dialysis in Patients with Perfused and Transplanted Kidneys

Weeks	Number of Patients
1	13
2	6
3	2
4	1
5 or more	1*
Total	23

*Acute cortical necrosis

The average duration of preservation of the twenty-three kidneys that developed ATN after transplantation was 21.8 hours which was not significantly different when compared to the whole group of preserved kidneys which had an average of 19.5 hours. The average values of LDH in the perfusate of these kidneys that developed ATN was initially 85 U% and increased to 160 U% at the end of preservation. These values were not significantly different from the group of kidneys with the same time of preservation. Thus, there was no direct relationship between the LDH levels and the presence of ATN.

Fifty-two of the seventy-seven patients (68%) had immediate function of their grafts (Table 4). Two years later, there are 55 patients (72%) who are well with functioning cadaver donor grafts. The 22 kidney losses were related to rejection, (10), sepsis (9), hyperkalemia (1), ureteral leakage (1) and one kidney never functioned.

TABLE 4
Renal Function of Patients with Perfused and Transplanted Kidneys

Immediate	**52 (68%)**
Delayed (ATN*)	**22 (31%)**
Never	**1 (1%)**

*(Required dialysis)

There were nine kidneys preserved for more than 30 hours before transplantation. One kidney was never transplanted. One recipient died 24 hours post-transplantation of hyperkalemia, and another died on the fourth postoperative day with hyperacute rejection. Five of the remaining six kidneys in this group required dialysis (83%). Following one to four dialysis, the serum creatinine began to return to normal values in all patients. Thereafter, a complete recovery of the

renal function was observed.

Eleven of the 84 transplanted kidneys had more than 20 minutes of warm ischemia. Eight of these kidneys were not used because of decreased perfusate flow, increased resistance, nonpulsation or thrombosis of the renal artery. Of the three kidneys that were grafted one patient had a kidney that functioned normally with a serum creatinine of 0.9 mg%, seven days postgrafting. The LDH at the end of organ preservation was 160 U%. Another patient had a serum creatinine of 9.9 mg% at seven days after transplantation. The LDH was 280 U% at the end of preservation. He required more than one dialysis, and finally he rejected on the 90th posttransplant day. On day 90, the rejecting kidney had a serum creatinine of 6.2 mg% and a transplant nephrectomy was performed. The last patient transplanted with a 20 minute warm ischemia kidney exhibited a serum creatinine of 7.8 mg% at one week after transplantation. He also required more than one dialysis. The LDH at the end of preservation was 280 U%. One month after grafting, this patient had a transplanted kidney with normal function.

Discussion

In cadaveric kidney allografts, warm ischemia (>20 min.) is the most important nonimmunological pretransplant event (preventable) that will determine the subsequent transplant renal function.[6] The presence of warm ischemia implies several other factors which may affect function, such as: (1) poor preoperative donor preparation, (2) prolonged preoperative hypotension, (3) poor handling of the kidney during surgery, (4) traumatic injury of the kidney and (5) rapid nephrectomy. Furthermore, the duration of preservation influences the outcome of the transplanted kidney. When preserved longer than 30 hours, most kidneys develop acute tubular necrosis. If kidneys are preserved no longer than 20 hours, no detrimental influence is made upon immediate subsequent function. From our data, it is apparent that both prolongation of perfusion and warm ischemic negatively influence the immediate outcome of kidney function after transplantation from cadaver donors.

The best viability signs during perfusion were perfusate pressure and pulsatile flow.[10] Most of the kidneys with decreased flow and increased pressure developed ATN after transplantation. The accumulation of LDH in the perfusate was also consistently elevated in ischemically damaged kidneys. The length of preservation did not necessarily correlate with high enzyme levels in the perfusate. The addition of phenoxybenzamine and methylprednisolone to the kidney perfusate determined an improvement of perfusate flow and pressure with decreased vascular resistance, but the kidney function posttransplantation was not significantly modified. Other factors, such as rapid en bloc dissection and satisfactory maintenance of the donor's fluid balance were essential to good kidney function.[6,9]

The incidence of perfused kidneys that were non-used for transplantation were considerably high (18%). Utilization of these kidneys could be improved by the development of a national organ procurement center that would offer a more reliable availability of recipients for transplantation. Regarding the utilization of ischemic kidneys, better perfusion techniques and organ metabolic support should be obtained in order to maximize the use of organs that otherwise will be eliminated for transplantation. Experimentally, we have observed that allopurinol protected ischemically perfused kidneys.[11] It is possible that its use in clinical preservation might eliminate some of the ischemic changes observed after transplantation.

The practical methods for prevention of warm ischemic damage during harvesting in the cadaver donor are various: (1) the maintenance of a stable cardiovascular status, (2) the establishment of a diuretic state with fluids or diuretics (mannitol 6.25 gm or furosemide 0.5-2.0 mg/K I.V.), (3) the use of membrane stabilizer agents (methylprednisolone, 30 mg/kg—120 min preoperatively), (4) a rapid non-touch dissection technique followed by immediate flush and hypothermic preservation and (5) the utilization of plasma perfusates with membrane stabilizer drugs (methylprednisolone or allopurinol). Other methods currently used in renal harvesting of cadaver donors include the utilization of α-adrenergic blockers, phenoxybenzamine (0.5-1.0 mg/kg-30 min preop.) or regitine (1.0 mg/kg) with variable results.[1,2,7]

With the use of successful perfusion techniques and better kidney histocompatibility typing, there seems little reason why cadaveric transplantation should not be brought up to a level of success

achieved at present in living related transplants. However, there are still several questions to be answered; the prolongation of renal preservation and the adequate treatment of ischemic kidneys. The utilization of new perfusates with practically no lipids or higher concentrations of proteins and increased osmolarity might improve the outcome of the preserved kidneys. Furthermore, the use of allopurinol, that protected ischemic canine kidneys during preservation, may improve the clinical outcome of ischemically damaged kidneys undergoing transplantation.

Summary

One hundred and eighteen potential cadaver kidneys in a period of twenty-three months were preserved by hypothermic pulsatile perfusion at the University of Minnesota. Ninety-seven (82%) of these kidneys were transplanted; the rest were eliminated mainly because of nonavailable recipients (7%) and warm ischemic damage (5%). Eighty-four kidneys were transplanted in seventy-seven patients at this medical center. Twenty-two kidneys (28%) were lost after transplantation chiefly due to rejection and sepsis. The rest of the grafted kidneys (72%) two years later are well with functioning cadaver grafts.

Most of the transplanted patients with kidneys that had more than 20 min. of warm ischemic damage or those that were preserved longer than 30 hours developed acute tubular necrosis. Thus, it is apparent that both prolonged preservation and warm ischemic damage negatively influence the immediate outcome of the transplanted kidneys from cadaver donors.

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Hepatocellular Carcinoma

A Clinical and Pathological Study of 33 Cases

V. TSAKRAKLIDES, M.D.*; A.C. TEMPLETON, MRCP (ED), MRCP ATH;†
R. ESTENSEN, M.D.‡ AND R. A. GOOD, M.D., PH.D.#

Thirty-three cases of hepatocellular carcinoma seen at postmortem are reviewed. The histological features, metastatic patterns, diagnostic problems and relationship to cirrhosis are discussed. A lower portion of cases developed in association with cirrhosis than reported in other areas. The incidence of this tumor in this autopsy population appears to have risen over the past 50 years. Two unusual cases are described, one of which presented with hypercalcemia and another in which the tumor developed in association with hemihypertrophy.

HEPATOCELLULAR CARCINOMA is an unusual tumor in America. It accounts for between 0.02 and 1.05 percent of autopsies at different institutions.[1-5] The lowest figure published is that of an earlier series from the Pathology Department of University of Minnesota; Clawson and Cabot[6] found only one case in 5,100 autopsies. Reports from this[7-9] and other institutions[10-12] have shown an increased incidence in recent years. The postmortem records of the University of Minnesota Hospitals were surveyed to determine the incidence and pathological features of hepatocellular carcinoma in this apparently low incidence area.

Material and Methods

The autopsy records of the University of Minnesota Hospitals from January 1954 to June 1972 were reviewed. This comprised a total of 12,070 cases. Hospital charts from these patients were surveyed, and available histological material was examined.

All cases of cirrhosis which came to postmortem during this same period of time were noted. These were classified into one of six types as recommended by Standard Nomenclature (SNODO). These were portal (Laennec's), primary biliary (hypertrophic Hanot's), coarse nodular (post necrotic), congenital, cirrhosis in hepatolenticular degeneration (Wilson's disease) and hemochromatosis.

Results

Thirty-three hepatocellular carcinomas were found. This comprises 0.27% of autopsies recorded 1954-1972. All patients were of the caucasian race, and 73% were males (males accounted for 58% of the total number of autopsies) with the peak incidence in the sixth, seventh, and eighth decades. Among older patients was a marked male predominance, while in younger age groups incidence in males and females was similar. Other primary malignant tumors of the liver seen during this period include two cases of adenocarcinoma of intrahepatic bile ducts and one hepatoblastoma in an infant; these tumors have been excluded from the study.

Presenting Features and Diagnostic Problems

The presenting signs and symptoms were abdominal pain and discomfort in 15 cases, hepatomegaly in six, jaundice in five and nausea and vomiting in four. Hematemesis was the presenting symptom in three, fatigue and weight loss in two and fever of unknown etiology in two.

The diagnosis was made prior to death in 16 instances. The presenting signs in the correctly diagnosed cases were abdominal pain in nine and hepatomegaly in five. Obstructive jaundice and

*Medical Fellow, Department of Pathology, University of Minnesota, Minneapolis, Minnesota.
†Professor, Department of Pathology, University of Minnesota, Minneapolis, Minnesota.
‡Assistant Professor, Department of Pathology, University of Minnesota, Minneapolis, Minnesota.
#Director and President, Sloan-Kettering Institute for Cancer Research, 410 East 68th Street, New York, New York.
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Please address requests for reprints to V. Tsakraklides, M.D., Sloan-Kettering Institute for Cancer Research, 425 East 68th Street, New York, N.Y. 10021.
See editorial, page 467.

hemorrhage into the gastrointestinal tract were the presenting feature in one case each. In three pediatric patients the presenting sign was an abdominal mass. In only one was the presenting feature a result of metastasis; in this case deposits in the cervical spine produced pain and weakness of the right arm.

In 17 patients the diagnosis was made only at autopsy. In four the hepatocellular carcinoma was an incidental finding and had not produced signs or symptoms. Two patients who presented with pyrexia of unknown origin had large necrotic tumors at autopsy. One presented with a history of cough precipitated by standing erect; at autopsy she had the largest tumor in this series (6.5 kgms). One patient presented with shortness of breath and had tumor growing along the hepatic veins and inferior vena cava into the right atrium.

One patient, a 39-year-old white female, who was referred to the hospital for evaluation of hypercalcemia had a history of unexplained nausea and abdominal pain. Skeletal survey was normal. Serum calcium was 15 mg% and PO_4 1.6 mg%. The patient underwent exploration of the neck; four normal parathyroids were found, and three were excised. Soon after surgery calcium levels returned to the previous high levels. Steroid administration caused a slight fall in level, but this rose following withdrawal and the level was not responsive to further administration. Mediastinal exploration was done, but no further parathyroid tissue was found. The fourth parathyroid gland was excised, but serum calcium levels remained high. Inappropriate parathormone secretion from an occult tumor was suspected, and celiac arteriorgraphy was suggestive of hepatic tumor although needle biopsy of the liver was negative. The patient died shortly afterward, and autopsy revealed a 13 x 7 cm. hepatoma in the left lobe of the liver. Small metastatic foci were in lymph nodes of porta hepatis, the diaphragm and one ovary.

The average duration from onset of symptoms to death was only 5.5 months; the longest interval was 18 months. Death was caused by gastrointestinal bleeding in 10 cases, hepatic coma in nine, pneumonia in seven, hepatorenal failure in five and was operative or postoperative in two.

Associated Findings

Associated diseases in these patients are shown in Table 1. Less than half had cirrhosis of the liver. Five had second primary neoplasms, three of which were central nervous systems (two glioblastomas and one mixed glioma). In two the hepatic tumor was found only at autopsy, and in the third case hepatic enlargement was noted three months after the cerebral tumor was diagnosed. The fourth patient had carcinoma of the esophagus and cirrhosis. The fifth had a squamous carcinoma of the mouth apparently cured by surgery and radiotherapy; three years later he developed an oat cell carcinoma of the bronchus which metastasized widely; at autopsy hepatocellular carcinoma was discovered incidentally.

TABLE 1
Associated Diseases in 33 Cases of Hepatocellular Carcinoma

	Number of cases
Cirrhosis	14
Second Primary tumor	5
Lithiasis of bile passages	4
Diabetes mellitus	4
Hyperthyroidism	1
Congenital hemihypertrophy	1
Lung tuberculosis	1
Pancreatitis	1
Ichthyosis	1
Syringomyelia	1
Porphyria	1
Gastric polyposis	1
Syphilis	1

One of the children with hepatocellular carcinoma was a five-month-old infant with multiple malformations including a hemihypertrophy, malrotation of the colon, atrio-septal defect, hemangioma and cafe au lait spots. The child was born at the 38 weeks gestation by Caesarean section. Birth weight was 11 pounds and ten ounces. At five months the baby was seen for anemia and hepatosplenomegaly. X-ray studies showed a mass in the liver; liver biopsy showed hepatocellular carcinoma. A right lobectomy was performed; the baby died during the operation. At necrosy the circumference of the left arm was 2 cm. larger than the right and the left leg was 2-3 cm. larger than the right. The left kidney was 70 gm. and the right 40 gm. The right lung weighed 50 gm. and the left 45 gm. The spleen weighed 50 gm. and heart, 45 gm.

Macroscopic and Microscopic Findings

Diagnosis was established by biopsy in 16 cases. Fourteen were performed during laparotomy, one at peritoneoscopy and one percutaneous needle biopsy was done. In three instances needle biopsy was negative although autopsy later revealed tumor.

The tumor was located predominantly in the right lobe of the liver in 14, and in the left in nine. In 11 there was almost complete replacement of both lobes. Grossly the tumor was nodular in 15 cases, massive in 13 and diffuse in five cases.

Metastases were found in 14 (53%) (Table 2). Patients with marked enlargement of the liver (more than 2.5 kgms.) had a higher rate of metastases than those with smaller tumors (64% compared with 53% overall). Involvement of hepatic or portal veins was seen in 11 cases (10 males, one female), not necessarily correlated with metastases; in one instance, tumor had grown along the hepatic vein, inferior vena cava and into the right heart without deposits in the lung. Patients with venous occlusion usually had marked ascites which was grossly hemorrhagic in four. Bilateral pleural effusion was present at autopsy in 45%.

TABLE 2
Distribution of Metastasis in 15 Cases of Hepatocellular Carcinoma

	Number of Cases
Lung	12
Lymph nodes	12
Adrenals	6
Diaphragm	3
Bone	2
Pancreas	2
Ovaries, spleen, kidney, stomach, pleura, dura, peritoneum	1

Relation to Cirrhosis

Fourteen of the 33 patients with hepatocellular carcinoma (43%) also had cirrhosis, a much smaller proportion than reported in other series.

During the period of this survey 400 patients with cirrhosis came to postmortem; the occurrence of hepatocellular carcinoma in this group was, therefore, 3.5%. The occurrence of cancer with the several types of cirrhosis is shown in Table 3. The occurrence was highest in males with the coarse nodular pattern (25%); in other types of cirrhosis it was much smaller. Patients with cirrhosis who died of hepatocellular carcinoma were older than those who died of other causes.

TABLE 3
Frequency of Hepatocellular Carcinoma in Various Types of Cirrhosis

Type of Cirrhosis	Number of Cases					
	Males		Females		Total	
	without ca	with ca	without ca	with ca	without ca	with ca
Portal	197	4	73	1	270	5
Coarse Nodular	36	7	45	—	81	7
Obstructive Biliary	2	1	4	—	6	1
Hemochromatosis	11	—	9	1	20	1
Lenticular Nuclear Degeneration	2	—	3	—	5	—
Congenital	2	—	2	—	4	—
Total	250	12	136	2	386	14

During most of the course of this survey, tests for Australia antigen and alpha feto protein were not available. Serum alpha feto protein was positive in only one of four cases tested.

Discussion

Hepatocellular carcinoma was found in 0.27% of autopsies at the University of Minnesota Hospitals, 1954-1972. This compares with 0.02% reported 1923[6] and is substantially higher than in subsequent reports.[7,8] The influence of possible patient selection is unknown although great interest existed in the Department of Internal Medicine in the study of liver disease during most of this period.

A possible source of bias is that the 1923[6] as well as subsequent reports[7-9] were based on all records filed in the Department of Pathology; about 15% of these were from the University Hospitals, and the remainder were from neighboring county and private hospitals.[9] Data from all reports from this institution[7-9,13] are shown in Table 4. The incidence of hepatocellular carcinoma appears to be rising slowly. The Table also shows that the incidence of cirrhosis as well as the incidence of liver carcinoma in cirrhotics has not significantly increased.

TABLE 4
Incidence of Hepatocellular Carcinoma and Cirrhosis

	Years surveyed	Autopsies #	Hepatomas %	Cirrhosis %	Hepatomas in Cirrhosis %
Clawson and Cabot	-1923	5,100	0.02	—	—
Higgins	1910-1933	12,581	0.09	2.9	3.0
Hebbel	1911-1962	114,757	0.21	1.3	3.4
Tsakraklides et al.	1954-1972	12,070	0.29	3.3	3.6

Our results suggest that the patients at particular "risk" were elderly males with coarse nodularity of the liver. Twenty percent of such patients were found to have hepatocellular carcinoma compared with none of 45 females with coarse nodular cirrhosis. The overall occurrence of hepatic cancer in cirrhosis is reportedly similar in other parts of the United States. Berk and Lieber[10] found 3.4% in 550 cirrhotics and Warren and Drake[14] four of 125 cases, although Stuart[15] in Chicago reported tumor in 15% of patients with cirrhosis.

In Africa higher rates have been reported: 40% in Mozambique and 17% in Uganda.[16] In South Africa, Becker and Chatgidakis[17] reported cancer in 44% of African cirrhotics but in only 6% of whites with cirrhosis. Macronodular cirrhosis is relatively much more frequent in Africa than in the United States.[18] Both macronodular cirrhosis and hepatocellular carcinoma are reportedly associated with Australia antigen in Uganda[19]; Australia antigen may be casually related to hepatocellular carcinoma. Reactivity to Australia antigen has been found in alcoholic cirrhosis[20] and the relation to carcinoma may be merely casual.

In most populations about 65-85% of hepatocellular carcinomas reportedly develop in association with cirrhosis.[1-5,11,21-23] In Minnesota less than half were associated with cirrhosis; this appears to be partly a result of low incidence of cirrhosis and the relatively low occurrence of tumors in cirrhotic livers, or could be related to the low overall prevalence of Australia antigen. In Minnesota cirrhosis carries a "risk" of developing cancer 10-12 times higher than the general autopsy population. Patients at greatest "risk" were males with coarse nodular pattern of cirrhosis. Other types of cirrhosis carried a smaller "risk" and only one of 20 patients with cirrhosis and hemachromatosis were found to have cancer.

An association of hepatocellular carcinoma with other tumors might be expected to occur by chance alone. Cancer of the esophagus, cirrhosis and hepatocellular carcinoma, as in one patient might be associated with alcohol consumption.[26] The association of glioma and hepatic cancer, as in three cases, is difficult to explain. Hemihypertrophy has been associated with nephroblastoma and in five cases with embryonal hepatoma.[27,28] We are aware of no reports of the association with hepatocellular carcinoma.

In one instance the tumor appeared to have secreted a parathormone-like substance. Hypercalcemia is a rare systemic manifestation of hepatocellular carcinoma in the absence of bone metastases[29,30] and has been shown in a recent report[31] to be due to the production of a parathormone-like substance.

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26-31 Will be on page 492.

Dextran 40 Anaphylaxis

EDWARD P. KRENZELOK, Pharm.D.* and WILLIAM A. PARKER, Pharm.D.†

A case report illustrating an anaphylactic reaction to low molecular weight dextran (dextran 40) is presented. The incidence, possible etiology, manifestations, and management of this adverse drug reaction are discussed.

LOW MOLECULAR WEIGHT dextran (dextran 40) is a mixture of glucose polymers having an average molecular weight of 40,000, with an approximate range of 10,000 to 80,000.[1,2] Production is through the bacterial conversion of sucrose by *Leuconostoc mesenteroides*.[3,4] Clinically, dextran 40 is most frequently used as a plasma volume expander, and for its effects upon the microcirculation and antithrombogenesis.[1,2,5] A relatively safe drug, dextran may, in rare cases, give rise to severe hypersensitivity reactions. Although more than 25 million units of dextran have been used since its introduction,[6] only 64 probable dextran-related cases of anaphylaxis have been reported.[6,7] Most of the anaphylactic reactions have occurred during the administration of medium and high molecular weight dextrans, with only an occasional, extremely rare case associated with the low molecular weight fraction. However, with the increasing clinical utilization of dextrans, one must gain an increasing appreciation of their potential antigenicity. The following case report illustrates an anaphylactic reaction to dextran 40.

Case Report

A 51-year-old white male was admitted to St. Paul-Ramsey Hospital with a diagnosis of skull fracture, subdural hematoma, and major motor seizures. Cranial surgery was performed three weeks after admission for evacuation of epidural and subdural spaces. Shortly thereafter the patient developed deep vein thrombosis. Considering the risk of a repeat subdural bleed with heparin anticoagulation, an alternative course of dextran 40 (Rheomacrodex) was instituted to prevent extension of the thrombus.

Dextran 40, 500 ml to be given intravenously over 12 hours, was begun. After having received approximately 2 ml of the infusion, the patient immediately complained of severe pain at the infusion site with burning and watering of the eyes and mouth. His face was markedly flushed and diaphoretic with cyanotic lips. Physical findings revealed a weak pulse with a rate of 100 beats per minute, blood pressure of 80/40 mm Hg, and dilated pupils. Although the infusion was immediately discontinued, the patient became less responsive. Breathing was deep and irregular, pupils dilated, and no blood pressure, carotid pulses or heart tones were detectable. Cardiac activity was restored by external cardiac massage, and supportive measures of oxygen and intravenous fluids were maintained. An erythematous rash was evident at the intravenous injection site.

The only other medication being taken at the time of the reaction was dioctyl sodium sulfosuccinate (Colace), 100 mg daily. The patient was eventually discharged without residual effect from the anaphylactic episode.

Discussion

The above case illustrates an example of dextran-induced anaphylaxis. Additional clinical manifestations which may be encountered include pruritis, urticaria, laryngeal edema/spasm, and respiratory arrest.[1,5] Although the above patient responded favorably without drug intervention, one should consider epinephrine (Adrenalin) the primary agent of choice in treating acute emergencies secondary to drug reaction. Rapidly acting, it stimulates both alpha adrenergic receptors, eliciting peripheral vasoconstriction, and beta adrenergic receptors, relaxing constricted bronchial musculature and reducing bronchial secretions and swelling. Antihistamines and corticosteroids may also be useful adjuncts.[8] Additional supportive measures may necessitate intubation, respiratory assistance, and/or maintenance of

*Instructor, University of Minnesota College of Pharmacy, Minneapolis, Minnesota.

†Assistant Professor of Pharmacy, Dalhousie University College of Pharmacy, Halifax, Nova Scotia.

blood pressure.

A recent survey (1962-1972) reports the incidence of dextran 40 anaphylaxis to be 1:300,000.[6] The higher molecular weight, highly branched molecules appear to greatly increase the incidence of reaction, possibly through heterogeneity and antibody production.[9-12] Several natural sources of dextran exist and may be responsible for providing prior exposure and sensitization to the antigen. Dextrans are known contaminants of commercial beet and cane sugars.[4,13] Similar polysaccharides are produced by certain bacteria, such as group H streptococci, pneumococci types II, XII and XX, and *Salmonella typhosa*.[4,14] Thus, patients with these infections may be more prone to dextran-reactions.[4] Prior sensitization may also occur from exposure to dextrans in the form of certain drugs, such as iron dextran (Imferon). Additionally, bacterial protein present in the commercial production of dextran may escape purification, hence serving as antigenic stimuli.[1] Confirmation of an allergic etiology is lacking, and current evidence suggests that the reaction may indeed be idiosyncratic. Patients having had infusions of dextran without adverse reaction have not shown any evidence of sensitization on subsequent exposure.[6] In most cases, skin tests placed on patients with documented dextran anaphylaxis are non-reactive,[14-15] and demonstrable antibodies to dextran cannot be found.[14] Although most theories involve dextran-induced histamine-release, there is presently no consistent evidence compatible with either an allergic or idiosyncratic etiology.

It is interesting to note that most of the anaphylactic reactions occurred in patients not under general anesthesia or stress conditions (shock, trauma, or surgery).[7,16] In a 14-year study by Bauer and Östling, anaphylactic hypotension occurred in only one of 8,336 surgical patients receiving dextran during the course of their operations, whereas nine of 4,090 patients given dextran preoperatively reacted with hypotension ($p < 0.0005$). Protective mechanisms, such as increased output of endogenous catecholamines in shock and elevated corticosteroid production during and post surgery, may have protected the above patients from dextran reactions.

Conclusion

With the increasing application of dextrans in medicine, one should familiarize himself with the potential adverse reactions to this substance. Anaphylaxis secondary to dextran administration is indeed very rare, but it should be anticipated, especially when administering the higher molecular weight fractions. These reactions usually occur early in therapy, and it is advised that the physician be present for the initial administration to stop the infusion and institute appropriate therapy, if necessary.[1] Despite the current controversy regarding the nature of the reaction, care should also be taken to obtain complete drug histories for previous dextran reactions.

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Physostigmine

Antidote for Anticholinergic Poisoning

BRUCE D. SNYDER, M.D.*

Physostigmine, a centrally acting anticholinesterase inhibitor, appears to be a safe and effective antidote for toxic delirium due to a variety of commonly used drugs. The effectively antagonized intoxicants include not only the Belladonna alkaloids but many psychoactive drugs not commonly thought of as exerting a significant atropinic effect. Experience suggests that physostigmine may be used as a diagnostic-therapeutic trial for the patient who presents with a delirium or coma and who is thought to have ingested one of these drugs.

A NUMBER OF COMMONLY used drugs with a diverse spectrum of clinical usage have significant anticholinergic (atropinic) side effects. In some cases, these side effects are simply extensions of the agents' primary therapeutic effect. In other situations, as for example with the anti-Parkinsonian drug trihexyphenidyl, atropinic effects are not desired or commonly experienced clinically and may be overlooked. Even groups of drugs such as the phenothiazines and the tricyclic anti-depressants, which are thought to effect primarily catecholamine transmitters of the central nervous system, produce such reactions as dry mouth or urinary retention in some individuals.

For the most part these atropinic side effects are easily dealt with and are not life-threatening. However, many of these agents can induce an anticholinergic toxic delirium similar to that of atropine. This is characterized by confusion, hallucinations, tachycardia, seizures and mydriasis. With higher dosage stupor, respiratory depression and finally respiratory arrest may result. A number of reports attest to the high morbidity and mortality of this situation.

Anticholinergic drugs competitively block the effect of acetyl choline (ACCH) at synapses by binding to the post-synaptic receptor. Raising the concentration of ACCH in the synaptic cleft leads to reversal of this blockade. This increase in ACCH concentration may be accomplished by the use of inhibitors of choline esterase, the enzyme present at the post-synaptic membrane which hydrolyzes acetyl choline into inactive choline and acetate.

*Assistant Professor of Neurology, University of Minnesota School of Medicine; Department of Neurology, St. Paul-Ramsey Hospital, St. Paul, Minnesota.

Of the choline esterase inhibitors available, only physostigmine acts both on central and peripheral cholinergic synapses.[1] Physostigmine possesses a neutral tertiary ammonium group which allows its passage across the blood-brain-barrier. Neostigmine and pyridostigmine, two other commonly used anticholinesterases, contain charged quaternary ammonium groups. They act peripherally on exocrine glands and on cardiac, striated, and smooth muscle. The latter agents are useful in the treatment of myasthenia gravis and reversal of paralysis due to nondepolarizing neuromuscular blocking agents such as d-tubocurarine.

The Table provides a partial list of drugs capable of producing central anticholinergic side effects[2] which have been reversed by physostigmine. Physostigmine would seem to be a logical first step in the emergency treatment of delirium due to unknown drug ingestion.[2] A therapeutic trial of physostigmine is safe; when effective, it is diagnostic of anticholinergic intoxication. Unfortunately, despite a number of reports in the literature, this use of physostigmine is little known. Standard texts either neglect it entirely or limit its use to treatment of overdose of the Belladonna alkaloids.[1] Reports of deaths due to agents on the list still appear with no mention of attempts to use physostigmine.[3]

Side Effects

Side effects of physostigmine include: (1) increased intestinal motility (frequently with diarrhea); (2) increased G.I. and tracheobronchial secretions; and (3) emesis. Parkinsonism may be exacerbated by it.[4] Some authors[2] recommended atropine in small doses to counter the peripheral

TABLE

Drugs and Chemicals Capable of Producing the Anticholinergic Syndrome[2]

Medications	Plants
Amitriptyline (Elavil, Triavil)	Amanita muscaria (although muscarine is present in minute amounts, major toxic effects are anticholinergic)
Anisotropine (Valpin)	Bittersweet (Solanum dulcamara)
Atropine	Black henbane (hypocyamus niger)
Belladonna	Black night shade (Solanum nigrum)
Benactyzine (Deprol)	Deadly night shade (atropia belladonna)
Benztropine nesylate (Cogentin)[11]	Jerusalem cherry (Solanum pseudocapsicum)
Chlorpheniramine (Ornade, Teldrin, etc.)	Jimson weed (datura stramonium)
Chlorpromazine (Thorazine) and possibly other phenothiazine derivatives[12]	Lantana (Lantana camara) (Also known as Red Sage, Wild Sage)
Cyclopentolate (Cyclogel)	Potato leaves, sprouts, tubers (Solanum tuberosum)
Desipramine (Norpramin, Pertofrane)	Wild tomato (Solanum carolinensis)
Dicyclomine (Bentyl)	
Ciphenhydramine (Benadryl)	
Doxepin (Sinequan)	
Glutethimide (Doriden)[11]	
Homatropine	
Hyoscine	
Hyoscyamus	
Imipramine (Tofranil, Presamine)	
Isopropamide (Darbid)	
Mepenzolate (Cantil)	
Methantheline (Banthine)	
Methapyrilene (Sominex, Compoz, Cope)	
Nortriptyline (Aventyl)	
Pipenzolate (Piptal)	
Propantheline (Probanthine)	
Protriptyline (Vivactil)	
Pyrilamine	
Scopolamine	
Stramonium (Asthmador)	
Trihexyphenidyl (Artane)[11]	

Many other antihistamines, antispasmodics, sleep aids, decongestants, analgesics, anti-parkinsonism agents and miscellaneous drugs, chemicals and plants may produce clinically recognizable anti-cholinergic findings.

Modified from Rumack[2] and reproduced with the kind Permission of the author and publisher of Pediatrics.

Unless indicated by reference number the drugs were listed in the original table by Rumack.[2]

cholinergic effects of physostigmine. Atropine, however, does enter the CNS and conceivably could act synergistically with an anticholinergic intoxicant. To control the effects of physostigmine we prefer an anticholinergic agent whose actions are confined to the peripheral nervous system, such as glycopyrrolate (Robinul[C]) or propantheline hydrobromide (Pro-banthine[C]). For the patient in coma it may be wise to intubate before giving physostigmine to avoid possible aspiration of emesis. Emesis is rare with the 1 or 2 mgm trial dose and has not been encountered in published clinical series (e.g. 5).

Physostigmine Dosage Schedule

In adults, 2 mgm of physostigmine can be given subcutaneously or intravenously; if there is no response this should be repeated in 10 to 20 minutes. Glycopyrrolate (.4 − 1 mgm) or propantheline (20 − 30 mgm) can be given if diarrhea or emesis occur. If effective, 2 to 4 mgm of physostigmine may be given every two to four hours depending upon the patient's condition. It is important to realize that physostigmine reverses the synaptic effects of anticholinergic intoxicants for a time but it *does not shorten their overall duration of action.* Patients will lapse back into coma, develop arrythmias, etc. as the physostigmine wears off.[6] For this reason, these patients should definitely be hospitalized and monitored carefully until they remain stable without physostigmine for at least 24 hours.

Rumack[2] has published a physostigmine dosage schedule for children: .5 mgm physostigmine slowly IV every five minutes until a total of 2 mgm is given or symptoms are relieved. Single doses of up to 8.6 mgm of physostigmine have been administered to adults therapeutically.[7] Overdoses of up to 1000 mgm have been survived without sequelae.[8]

Other modes of therapy for anticholinergic intoxication have not proven successful. Arrhythmias in particular, are very refractory to conventional therapy but respond to physostigmine.[9] Ketchum, et al.[10] demonstrated that phenothiazines potentiate anticholinergic delirium; they also demonstrated that methylphenidate (Ritalin) had no effect on scopolamine intoxication. Forced diuresis or dialysis are not useful in removing many of these drugs as they are rapidly bound to tissue.

See references, page 477.

Asbestos in Duluth Water

ARTHUR H. WELLS, M.D.*

Extensive studies, mainly by EPA and its National Research Center, have found that nearly all of the asbestos in Duluth's tap water can be removed by flocculation followed by granular media or diatomaceous earth filtration. This can be accomplished at an estimated cost of five million dollars and will require two years.[59]

DURING THE LAST DECADE there has been a revelation of an occupational hazard of disastrous proportions, a hazard that involves workers exposed to the inhalation of asbestos fibers. This disclosure has stimulated an unprecedented worldwide explosion of literature on the hazards of asbestos.[1-9] The universal recognition of the slowly progressive and irreversible injuries[10-12] to many thousands of asbestos workers was long delayed in coming and the usual response of management has been described by some as callous and evasive.[13] The present day exposure of a large population† to drinking water with a very high concentration of asbestos fibers meets with a similar refusal of Mining Company officials at Silver Bay, Minnesota to admit any possible danger or accept any responsibility.[14]

One might wonder if there is a parallel between the now historic plight of asbestos workers of the past and the people of the Duluth area today.

Today, although there is no agreement as to the exact mechanism of its carcinogenesis,[15-20] no one in authority questions the fact that inhaled asbestos fibers frequently cause pulmonary fibrosis and malignancies of the lung and of pleural and peritoneal surfaces, generally after a 25 year or more period.[21-26]

Cancers of the Gastrointestinal Tract (GIT)

There are five independent group studies revealing a three-fold increase in malignancies of the gastrointestinal tract (GIT) in asbestos workers compared to unexposed people.[27-32] There can remain little doubt that asbestos can cause carcinoma of the esophagus, stomach, colon, and rectum. Whether the fibers from the lungs arrive at the site of these cancers by way of the blood stream or by the inevitable (except for loss in sputum) passage of possibly 98 percent of the inhaled fibers down the intestinal tract[33] is an unanswered question. Large numbers of asbestos fibers have been demonstrated in the gut walls of asbestos workers years after their exposure.[34] Excessive suspensions of asbestos placed in the stomach of lower animals have been demonstrated in large numbers in the blood stream and internal organs, possibly never to escape the body.[35-36] The larger asbestos fibers of 23μ or more in length must pierce the GIT wall by pinocytosis, while smaller fibers could be absorbed by persorption, as are large starch granules.[37]

Mesotheliomas

Of unusual interest in a selected literature on the subject of asbestos and mesotheliomas is: (a) the long latent period; (b) a frequently brief exposure time; (c) a preference of location in the peritoneum;[38-41] (d) a powerful carcinogenesis; and (e) an uncanny migratory property of asbestos fibers in research animals.[42-44] These authorities describe a latent period of from 15 to 59 years (an average of 30 years) between exposure and the development of the malignancy. The only exposure to asbestos in a few adults with mesotheliomas was a brief period of years in childhood playing outdoors near an asbestos manufacturing plant. An illustrative case is a 68-year-old man found to have a pleural mesothelioma at autopsy at the Miller-Dwan Hospital, Duluth. His only exposure to asbestos was a two-year period when he worked as a pipe coverer in a shipyard during World War II.

There are also twice the number of mesotheliomas of the peritoneum, compared to pleural surfaces, in asbestos workers. Does this occur by extension of fibers through the gut wall or from

*Department of Pathology, Miller-Dwan Hospital, 504 East Second Street, Duluth, Minnesota.

†Duluth, Superior, Cloquet, Two Harbors, Silver Bay, and Beaver Bay.

the lungs through the diaphragm or by the blood stream?

Duluth Tap Water

On June 15, 1973, the Federal Government's Environmental Protection Agency (EPA) first announced finding a high concentration of asbestos fibers in Duluth tap water.[45-46] Since then the National Water Quality Laboratory (NWQL) of Duluth and other federal agencies have been continuously studying the nature, source, concentration, and treatment of the asbestiform amphibole fiber laden water. They have proved to their own satisfaction that the fibers emanate from a crushed and ground cummingtonite-grunerite mineral[45-47] used in the process of making taconite pellets at Silver Bay, Minnesota. Sixty-five thousand tons of waste with 10,580,000,000 fibers per liter (450x) are discharged into western Lake Superior daily. They find an almost continuous counterclockwise current pushes the delicate asbestos fibers westward down the north shore to the west point of the lake, then eastward along the south shore. The amphibole fiber count at Duluth ranges from 20 to 70 million per liter by electron microscopy. The spring and late fall storms greatly agitate the waters and increase the count. X-ray spectroanalysis by electron microscope reveals these fibers to be amosite asbestos with the acknowledged equal pathogenicity[48] of the other two major commercial sources of asbestos (chrysotile and crocidolite).[49] Additional extensive daily studies of the NWQL failed to reveal any other sources of amosite fibers in the water of contributing streams or other parts of the lake. Each fiber in Duluth's water is identified as to its amosite spectrum before being counted. Should the dumping of this waste into Lake Superior be discontinued today, Dr. Philip Cook of NWQL estimates that it would probably require decades for the fibers to disappear from the water.[50]

Mathematics of a Potential Hazard

Of basic importance is the question, How does the number of amosite fibers ingested by Duluthians compare with those same fibers inhaled by workers who have developed gastrointestinal cancers in excess of the norm? The present day variations (±50%) in the counts of amphibole fibers in the same test samples of Duluth water by seven authoritative laboratories in the U.S. is one of several variables and unknowns which make comparing the number of fibers inhaled by workers in an asbestos plant with the number ingested by Duluthians a task which will yield results of debatable accuracy.

Dr. William J. Nicholson, an internationally recognized authority in the field, has shown a greater number of ingested fibers by Duluthians during the last 17 years compared to those inhaled by an occupational group over a one year period.[51] Nine hundred and thirty-three men showed a greater than twofold increase in GIT cancer over a five-year period in spite of the fact that 60% worked for less than one year. His formula is: 150 x 10^6f/m^3 x 8m^3 inhaled/day x 250 days = *3 x 10^{11} inhaled fibers per year.* For Duluth water ingestion his formula is: 5 x 10^7f/L x 2L ingested/day x 365 days/year x 17 years = *6 x 10^{11} fibers ingested.*

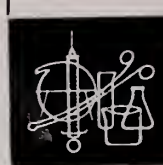
We choose to use the figures relating to a group working within the strict legal limits of two fibers per cubic milliter (450x) of air inhaled in England. These asbestos workers have been recently shown to have developed the asbestos related cancers by Dr. Hilton Lewinsohn of London.[52] Our formula for fibers inhaled by these workers is: 2f/mL^3 x 3[(53)] x 1000 x 0.8L/breath x 20/min x 60 min/ hr x 8 hr/day = *46 million fibers inhaled (and not exhaled) in one day.* For the number of fibers ingested per day by Duluthians the formula is: 5 x 10^7f/L x 2L ingested/day = *100 million fibers ingested in one day.*

Recent mortality studies of the Duluth area[54-55] revealed no increase in malignancies of the GIT after 14 and 17 years' exposure to the amosite asbestos laden Lake Superior water. Public health scientists will have an invaluable addition to their knowledge when the same mortality study is taken after 10 and 20 years with or without additional exposure to the unfiltered potable water of Duluth. There is a universal problem as to just how little asbestos is too much, whether ingested or inhaled. It has been found that practically everyone in large cities has asbestos fibers in his lungs.[56] Many of our drugs, beverages, city water supplies, ambient air, and beer contain significant amounts of asbestos.[57-58] In Duluth these sources only add to those from humidifiers, dried clothing, the water and other sources.

References will be found on page 488.

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Indications: *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

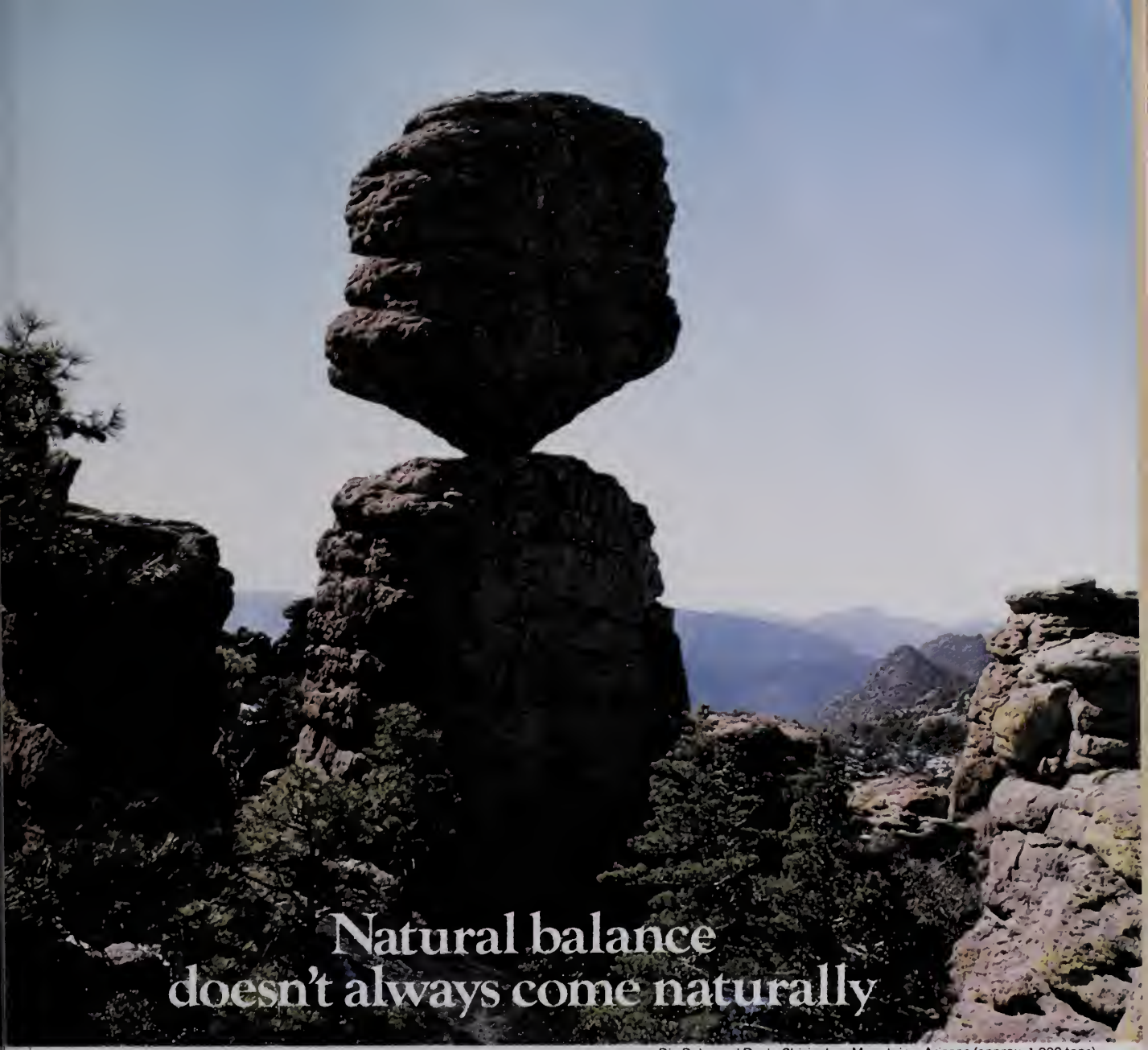
Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

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SUMMARY OF PRESCRIBING INFORMATION

DICATIONS. Based on a review of this drug by the National Academy of nces—National Research Council and/or other information, FDA has classified ndications as follows:
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nal classification of the less than effective indications requires further stigation.

CONTRAINDICATIONS. Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

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Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

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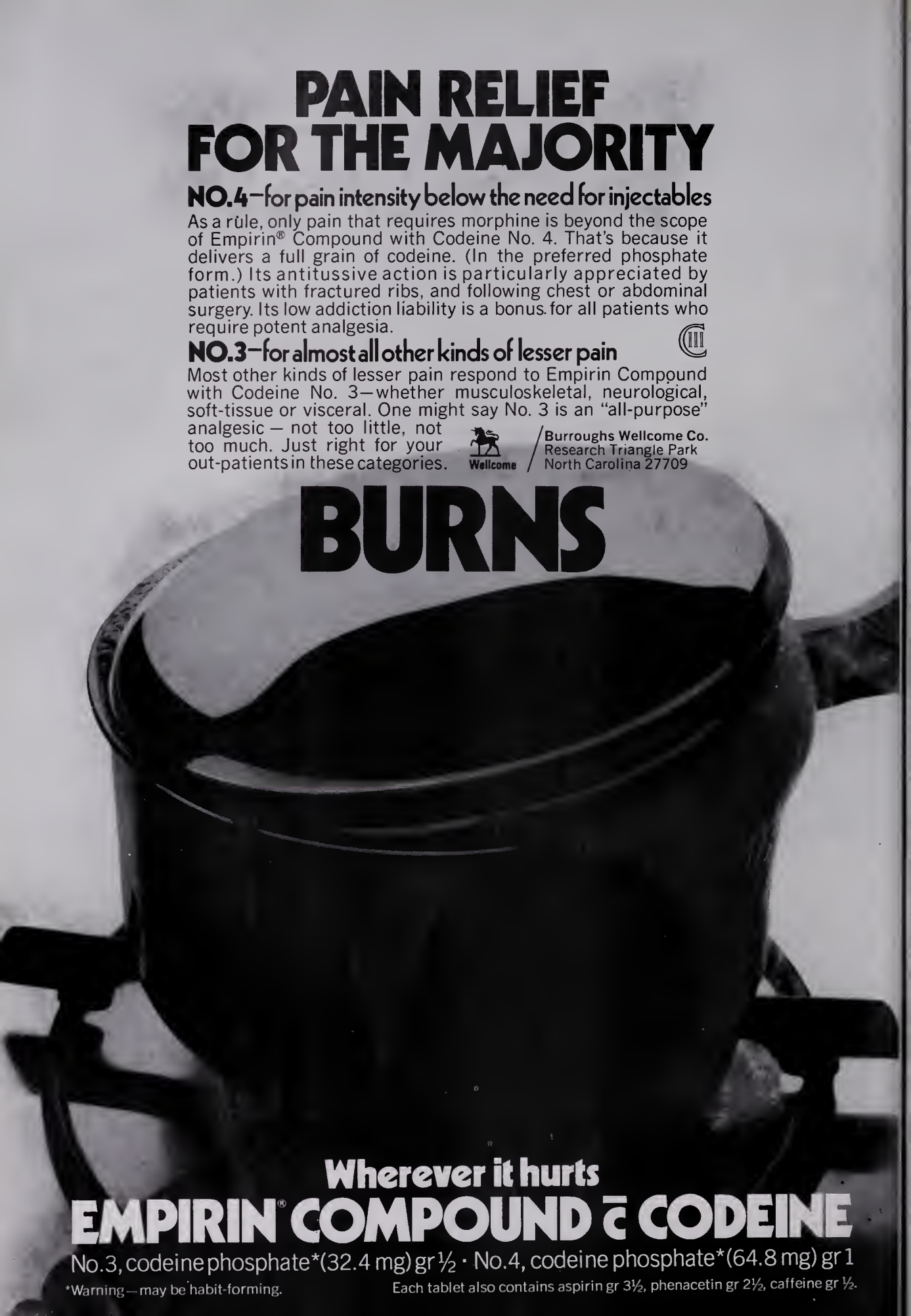
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Editorials

Practical Virology

In the May issue of Minnesota Medicine is an article "Practical Virology." Dr. Henry Balfour* of the publication received his practical training in virology in the Department of Health, Division of Medical Laboratories. We are pleased that he brings to the practicing physician's attention, methods of collection and submission of specimens and some of the rudiments related to interpretation of the laboratory results. These are in general agreement with our promulgations since 1953 when the writer of this editorial published similar information in Minnesota Medicine.† For a readily available updated reference regarding collection and submission of specimens, tests available and interpretation of results, I refer you to the back of the data forms which are in the containers supplied by the Minnesota Department of Health. The containers for submission of specimens are available from the Minnesota Department of Health, Division of Medical Laboratories, 717 Delaware Street S.E., Minneapolis, Minnesota 55440.

It should be noted that in most cases involving serologic tests, the results will be primarily useful in making a diagnosis in retrospect because of the necessary time interval (two to four weeks) between the collection of the first and second blood specimens. It is important that the first whole clotted blood specimen be sent promptly after collection to the Department of Health laboratory for storage until the second blood specimen is collected. Antibodies deteriorate with time unless the blood serum is frozen preferably at −20°C. Caution must be exercised in the interpretation of a "four-fold decline in titer," as opposed to a "four-fold rise in titer," which is more characteristic of an active infection.

Specimens collected with swabs from the throat or rectum for virus isolation may be submitted in trypticase soy medium, but this medium supports the growth of bacteria while the specimen is in transit. Hank's solution for transport of swab specimens or the "Handi-Swab" are preferred. Stool specimens are recommended over rectal swabs for virus isolation. It is imperative that specimens for virus isolation be sent to the laboratory with the least amount of delay. If the specimen is collected over the weekend, it should be held in the refrigerator until Monday morning for sending through the mail. Technical developments for the identification of viruses will soon make possible more rapid reporting of results.

Much progress has been made over the past 25 years in Minnesota in the identification of viral disease entities and prevention of viral infectons. It is not common knowledge that the Division of Medical Laboratories pioneered in the development of oral polio vaccine and discovered the trivalent oral polio vaccine. There hasn't been a single case of polio reported in Minnesota since 1966. The advances of virology in Minnesota were made cooperatively with the practicing physicians in the State and have resulted in better medical care for the citizens.

Henry Bauer, Ph.D.‡
Minneapolis, Minnesota

*See page 421.
†Vol. 36, pp. 1257-1259, 1953.
‡Director, Division of Medical Laboratories, 717 Delaware Street Southeast.

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Hepatocellular Carcinoma

The paper by Tsakraklides et al.* has many similarities with previous surveys of liver cell type carcinoma, namely the low incidence in Caucasian population and the increase in recent decades as shown by the Boston City Hospital and the Henry Ford Hospital survey. Of further emphasis is the parallelism with previous studies regarding cirrhosis, and in particular with the striking association of postnecrotic cirrhosis and hepatoma.

All of the above relationships are thought-provoking when one conjectures from these facts regarding etiologies of hepatoma.

The remarkable geographical variations deserve weight when considering the infective interplay, particularly regarding viral exposure. Australia antigen anemia, parasite infestation, aflotoxin, and hepatotoxic exposure.

Does cirrhosis play a formative role or is it a further expression of a concomitant pathogenesis?

Thus, this article again brings to our realization that the etiology of cirrhosis and hepatoma still eludes us, but incidence, correlation, and association are seeds of thoughts of possibilities and, thus, I enjoyed it.

R. W. Hughes, M.D.
Mayo Clinic

*See page 450.

Factors Determining Early Kidney Function

The present issue of Minnesota Medicine* contains a report from the University of Minnesota Transplant Team, Toledo-Pereyra et al., detailing results of cadaveric transplantation using pulsatile perfusion to preserve the kidneys. This report indicates the excellent results in transplantation that we have come to expect from their institution. In their hands pulsatile perfusion has been an effective means of preserving cadaveric kidneys for periods up to 30 hours. While their rate of acute tubular necrosis is unusually high as compared to that seen at our institution and others, their long term results show no deleterious influence therefrom.

Readers should be aware, that there is an increasing body of evidence, at least on a wide experience reported by Terasaki and others, that cadaveric kidney survival is significantly improved by using simpler methods of preservation such as flush and storage in Sack's solution. These data suggest that the longer the period of perfusion or preservation, the greater the antigenicity of the preserved kidney. This results in a higher rate of rejection in those kidneys perfused for longer periods of time, and especially by pulsatile perfusion.

Despite wide experience clinically and in the laboratory with this type of perfusion, at our own institution, we are making two changes with regard to cadaveric transplantation: (1) Every effort is being made to transplant cadaveric kidneys as soon as possible after they have been secured. (2) Soon preservation of cadaveric allografts will be carried out by the much simpler and less expensive method of a flush and storage in intracellular type solution such as Sack's. The drawbacks to the latter are: Less consistent success in preservation for periods of time over 16 to 24 hours, and the lack of any effective means of assessing kidney function once the organ has been harvested. We believe this will be an increasing trend in the future.

Again, my congratulations to the University for their excellent results.

John E. Woods, M.D.†
Rochester, Minnesota

*See page 446.
†Coordinator of Transportation, Mayo Clinic.

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Food Allergy in Atopic Dermatitis

ATOPIC DERMATITIS is one of the most common dermatologic problems in childhood. However, identification of the etiologic factor and the causative mechanisms remains enigmas. Diagnosing and treating this type of dermatitis is usually restricted to that of dietary manipulation, topical therapy of the existing dermatitis, and removal of local initiating factors.

If one considers two of the variables of atopic dermatitis, namely the skin itself and the immunologic apparatus, it becomes apparent that we know much more about the skin variable. We know that their skin is drier, is more easily aggravated by topical irritants, such as soaps, has a different pH in various sites, and responds differently to local pressure, i.e. delayed blanch phenomenon.

We have more uncertainties about the immunologic variable. Patients with atopic dermatitis have a higher incidence of asthma and allergic rhinitis. They usually have an elevated serum IgE level and many positive "allergy" skin tests but it is difficult to implicate these in the etiology. There is a lower incidence, from the general population, of contact dermatitis such as poison ivy, and they are usually less reactive with delayed hypersensitivity tests.

The observation made by Dr. Walsh in the April issue of MINNESOTA MEDICINE* regarding positive patch tests to foods is most interesting and further, this form of testing was apparently of benefit in deciding appropriate dietary management. As the author points out, we are anxiously awaiting further data regarding the role of the delayed or cellular type hypersensitivity mechanism in this condition. As we obtain more information with this and other mechanisms, we will be able to better judge the role of the immunologic system in atopic dermatitis and come to an understanding of how foods, at times, are etiologic agents.

E. J. O'Connell, M.D.†
Rochester, Minnesota

*See page 310.

†Department of Pediatrics, Mayo Clinic, Rochester, Minnesota.

Intussusception - A Continuing Problem

THE RECENT ARTICLE by Hugh J. Williams, Intussusception—Facts, Fallacies and Practicalities,* was most welcome in that it focuses attention on this clinical condition that continues to cause significant morbidity and even an occasional fatality. Most of these tragedies or near tragedies could be avoided, as the author points out, by a higher degree of suspicion and the institution of the appropriate diagnostic and therapeutic measures at an earlier stage in the course of the illness.

The first fallacy to be pointed out was the impression that many of us received in our earlier medical education that intussusception regularly presented with a characteristic clinical picture of intermittent cramping abdominal pain with associated current jelly stools. I'm sure that the greatest number of problems that occur in the management of patients with intussusception could be eliminated if this myth were dispelled and if intussusception were more often considered in patients with nonspecific abdominal symptoms and findings.

I support the author's recommendation of early barium enema, with the safeguards outlined, both for diagnosis and treatment. I also completely concur with his preference for a hydrostatic reduction of the intussusception over surgical management. I take minor exception to his concerns of "significant incidence of late mechanical intestinal obstruction due to post-surgical adhesions," and his concern of resection performed on bowel that is mistakenly felt to be "nonviable."

The incidence of mechanical obstruction due to adhesion in the properly performed laparotomy should be exceedingly low and there should not be a problem in differentiating viable and nonviable bowel to the experienced surgeon. Certainly these very sick children that do require surgery deserve this degree of expertise in their management.

All in all, the article is most appropriate and timely, and it is strongly recommended to all who are involved in the care of infants and young children.

John F. Waldron, M.D.
Minneapolis, Minnesota

*February issue, MINNESOTA MEDICINE, 1975, page 140.

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Philosophical Musings

It's Gotta Be True

"It must be true, it's there in black and white." My wife, a firm believer in the invincibility of the written word, had so often clinched an argument with the declaration that I had become almost powerless to refute what appeared to be a factual vital statistic.

One morning I opened the newspaper to find—in black and white—that I was dead! Deceased! That I had been, among other things, a Minneapolis resident for many years. I didn't even know that I had died! I knew I was eligible, though. I had become a Senior Staff man. I had been retired to the status of Editor Emeritus; I had been the beneficiary of a few Social Security checks; the kids had remembered my birthday; my Last Will and Testament had been recently amended, and my heirs legally specified; so what was there to do but accept my demise gracefully, which I proceeded to do.

I went to the kitchen for a glass of cold water and—to my amazement—discovered that angels drink water. I must admit that I thought being an angel would be much more glamorous: not just routinely and mundanely terrestrial. Rather, heavenly. I proceeded just as I had been doing when I was alive: I drove to work, waved a greeting to the bearded barber after parking my car, and said a happy good morning to the girls in the office. Then I sat down and attacked my pile of current manuscripts as a prelude to embarking on my usual strenuous professional program as physician and surgeon. In spite of occasional provocations to become irritable or impatient, I carried on all day with angelic imperturbability.

That night, in spite of or because of being defunct, I slept soundly—like an angel, in my newly acquired role. Naturally! Fresh as a daisy, I arose the next morning, determined to carry on as best I could, shifting my angel wings and halo with what I considered the correct celestial aplomb. With my extra cup of hot breakfast coffee I sat down to read about the pedestrian activities of my friends: those earthly and still mortal creatures! To my amazement, there in black and white, I read that there had been a serious error, apologies were being offered: an obituary that had been in galley for a long time was being retracted. But whose? I hastened on. It began to sound vaguely familiar. Perhaps a friend of mine?

But no! Believe it or not, it was me! I was alive? Not dead after all? Shucks! Well, it had to be so; it was right there in black and white.

What's more, there was nothing to do about it, so I went back to my sublunary chores of scorching the breakfast toast, scraping it off, eating my breakfast, and then carrying out the garbage for my wife. Heck!

Carl O. Rice, M.D., Ph.D.
Editor Emeritus

Letters to the Editor

We would like to encourage physicians to contribute to the Letters to the Editor Section. We want to hear what you have to say, what you think, why you hold certain opinions. In short, we want to make this as lively and spirited a section as possible.

The Editors

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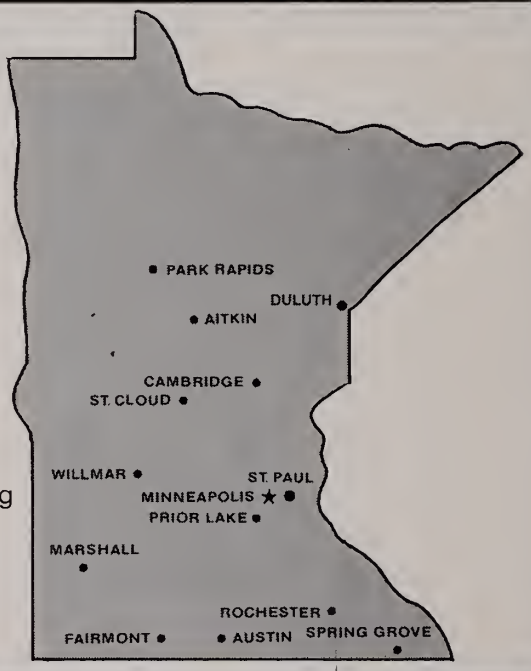
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Special Article

Role of Physiological Modifying Factors in Interpretation of Arrhythmias

KYUHYUN WANG, M.D.*; FREDARICK L. GOBEL, M.D.* and HAROLD G. RICHMAN, M.D.*

Interpretation of cardiac arrhythmias is facilitated by understanding the modifying effects of both automaticity and physiologic refractory period.

AN ARRHYTHMIA is usually regarded as a disturbance in either impulse formation or impulse conduction or both. Although these abnormal processes initiate the primary rhythm disorder, the ultimate manifestation of the arrhythmia is often determined by physiologic properties of the cardiac tissue. The most important of these are refractoriness and automaticity. These modifying factors often complicate the interpretation of an arrhythmia.

Refractoriness

The QRS complex in the surface ECG reflects only the early portion of the ventricular transmembrane action potential, and the refractory period extends for a considerable time following the QRS complex (Figure 1a). A similar relationship exists in depolarization of the atrium and the A-V junction. The nature of the conduction of any given impulse depends in part upon its temporal relationship to the refractoriness normally developed in various parts of the cardiac tissue by the previous impulse. Thus, an atrial premature beat (APB) will not be conducted antegrade if it occurs when the junctional tissue is still refractory; and it will then be inscribed on the ECG as a nonconducted APB (Figure 2). If an APB occurs at a time when the A-V conduction system is in a relative refractory period, ante-

*Cardiology Sections, Mt. Sinai Hospital and Veterans Administration Hospital; and Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota.
Address for reprints: Harold G. Richman, M.D., Cardiology Section, Veterans Administration Hospital, 54th Street and 48th Avenue South, Minneapolis, Minnesota 55417.

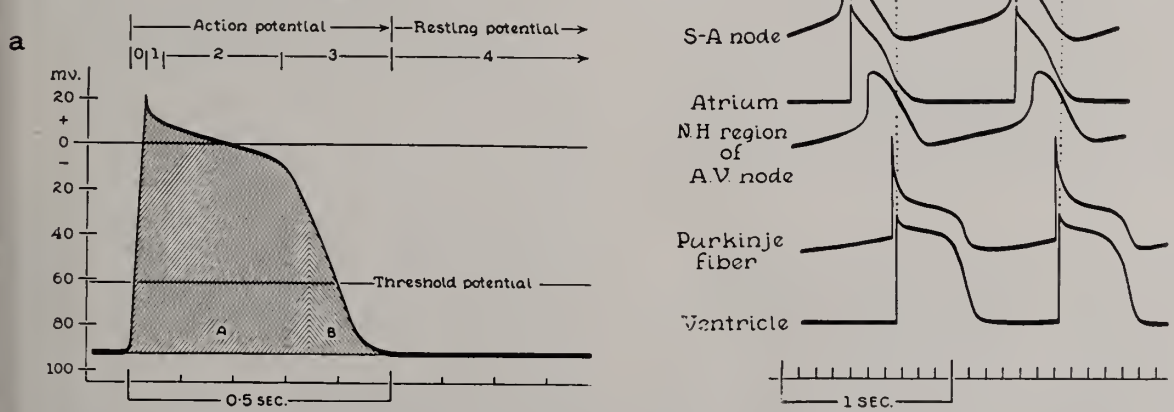


Fig. 1 (a)—The time-potential curve during depolarization of ventricular muscle cell is subdivided into four phases (0, 1, 2, 3). The resting potential is phase 4. The absolute refractory period (A) includes phase 0, 1, 2 and the first portion of phase 3, whereas the later portion of phase 3 is only relatively refractory (B). 1 (b) The time relationship between the electrocardiogram and the intracellular electrical potentials in five tissues of the heart during two sinus beats. The pacemaker cells in S-A node, N-H region of the A-V node and His-Purkinje system do not maintain constant resting potential. Instead, the resting potential slowly and spontaneously declines (diastolic depolarization). When it reaches the threshold potential, the cell develops action potential, thus acting as a pacemaker cell. The S-A node has the greatest rate of diastolic depolarization and reaches the threshold potential ahead of any other pacemaker cells in the normal state. Thus, the S-A node acts as a dominant pacemaker in the normal state.
(Reproduced with permission from "Cardiac Arrhythmia, Physiologic Principles" by SA Briller, Cecil-Loeb Textbook of Medicine, edited by PB Beeson and W McDermott; W. B. Saunders & Co., Philadelphia, 1971.)

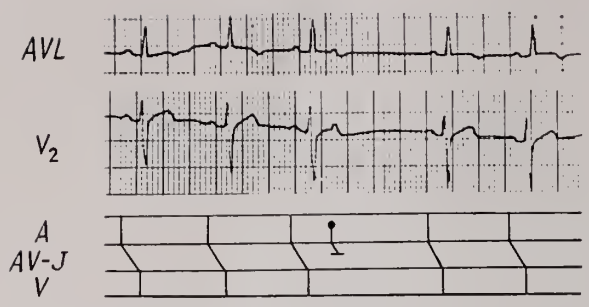


Fig. 2—The third QRS complex is followed by an APB which occurs during the absolute refractory period of the junctional tissue and results in a nonconducted APB. The primary disorder is an APB which is modified by the refractory period resulting in a nonconducted APB.

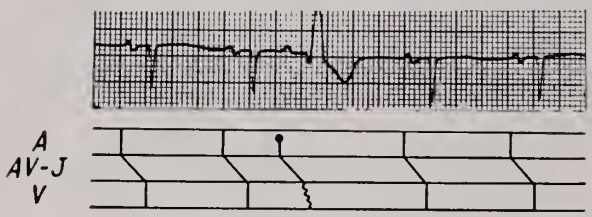


Fig. 3—The second QRS is followed by an APB which occurs during the relative refractory period of the conduction system. This results in both a prolonged PR interval and an aberrant conduction. The primary disorder is an APB which is modified by the refractory period resulting in a prolonged PR interval and an aberrant conduction.

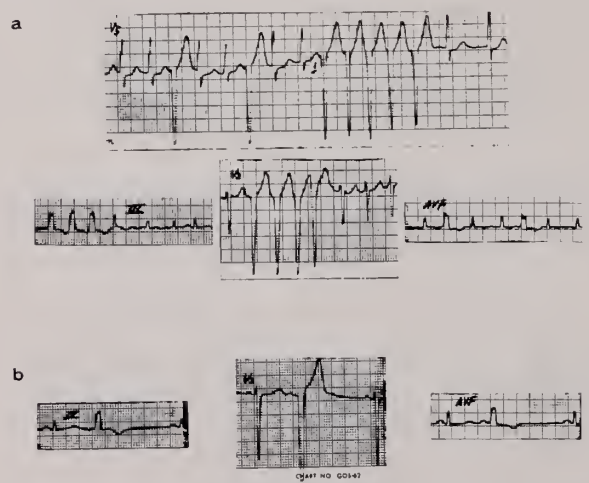


Fig. 4(a)—Atrial fibrillation with a ventricular rate of about 170 beats/min. Many abnormal QRS complexes raise the possibility of VPB's and ventricular tachycardia. (b) When a normal sinus rhythm was restored the following day, there were many APB's with aberrant conduction which have the same configuration as those in the corresponding leads in Figure 4a. This suggests that the abnormal QRS complexes in Figure 4a were also aberrantly conducted beats. The primary disorder is atrial fibrillation with a rapid ventricular rate which is modified by the refractory period resulting in an aberrant conduction.

grade conduction to the ventricle may be modified in various ways. If conduction through the upper A-V junction is the limiting factor, a prolonged P-R interval will be inscribed. If conduction delay is related to the bundle branches, the QRS morphology will be distorted resulting in an aberrant conduction (Figure 3). In a patient with atrial fibrillation, if the refractory period of the A-V node is shorter than that of the bundle branches, atrial impulses may be conducted to the ventricle when there is a differential refractoriness of the bundle branches and aberrant QRS complexes result. This may simulate runs of premature ventricular beats (VPBs) (Figure 4). Criteria for the differentiation between aberrant conduction and VPBs[4] may not be helpful in individual cases. Factors strongly in favor of aberrant conduction are irregular R-R intervals and, especially, disappearance of the abnormal QRS complexes when the ventricular rate slows with carotid sinus massage. At times one has to resort to a more definitive procedure such as His bundle electrography (Figures 5a and b).

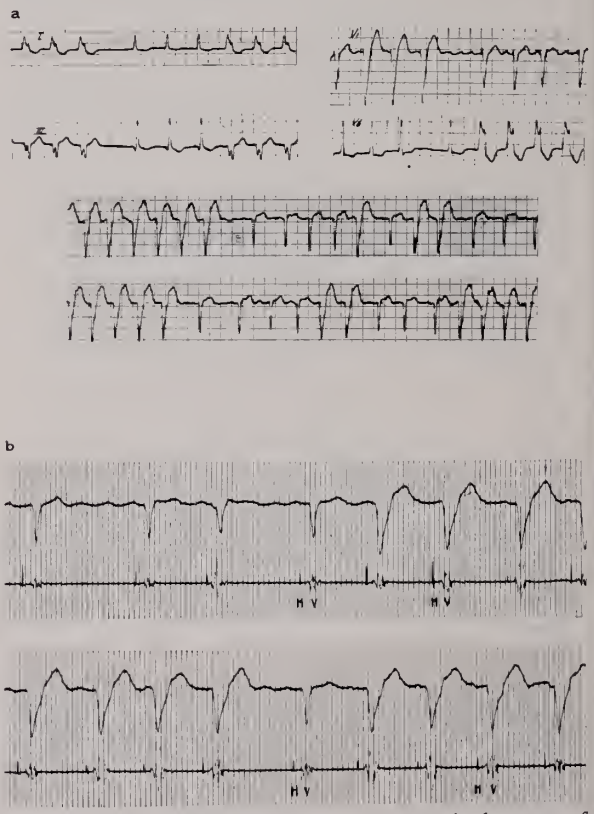


Fig. 5(a)—Atrial fibrillation with a ventricular rate of about 150 beats/min. Many abnormal QRS complexes raise the possibility of VPB's and ventricular tachycardia. (b) His bundle electrogram in this patient reveals a His bundle deflection in front of every QRS complex and confirms aberrant conduction.

Awareness of refractoriness helps to understand the manner in which VPB, a simple primary disorder, may precipitate a complicated arrhythmia. In the majority of instances, VPB occurs when A-V junctional or atrial tissue are refractory as a result of depolarization by an antegrade sino-atrial (S-A) nodal impulse. The antegrade atrial impulse in turn is not conducted to the ventricle because the latter is still refractory from the VPB and momentary A-V dissociation then results.[3] In this way, the sinus rhythm is not interrupted, and a subsequent sinus beat occurs at the expected time and a full compensatory pause results (Figure 6). If the atrial impulse arrives at the A-V junction when it is only partially refractory, ventricular depolarization may result after a prolonged P-R interval and/or result in aberrant conduction (Figure 6). The Wenckebach phenomenon shown in Figure 7 is a secondary response to the VPBs which have created a period of relative refractoriness in the A-V junctional tissue by concealed, retrograde conduction to the A-V junction. Pseudo A-V block in the form of Wenckebach phenomenon as described above can also occur secondary to concealed premature A-V junctional beats.[2,6] Thus, a simple primary disorder such as



Fig. 6—In the upper tracing ventricular bigeminy is apparent. Following each VPB, there are clearly visible P waves with a regular P-P interval revealing an uninterrupted sinus rhythm. These atrial impulses occur during the refractory period of the A-V junctional tissue because of the concealed retrograde conduction from the VPB's and are therefore not conducted to the ventricle. Thus a full compensatory pause results. In the lower tracing, the P waves following the VPB's occur during the relative refractory period of the conduction tissue and are conducted to the ventricle in an aberrant manner. There is no compensatory pause and an interpolated VPB's result. The primary disorders are VPB's which are modified by the refractory period of the conduction tissue resulting in interpolated VPB's with aberrant conduction of the following conducted beats.

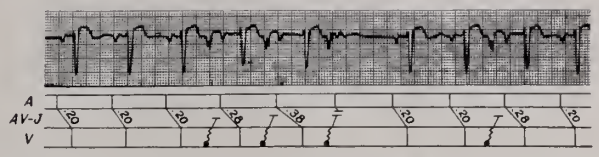


Fig. 7—VPB's with concealed retrograde conduction to the A-V junction render the latter relatively refractory in such a way that each S-A nodal impulse is conducted to the ventricle with progressively longer P-R intervals until an impulse is completely blocked. The primary disorders are VPB's, which are modified by the refractory period of the conduction tissue resulting in pseudo A-V block in the form of Wenckebach phenomenon.

VPBs may result in the inscription of a complicated arrhythmia.

The manifestation of A-V junctional rhythm may also be influenced by refractoriness (Figure 8). When a spontaneous A-V junctional impulse occurs before atrial depolarization from the S-A node, it may be conducted retrograde and "capture" the atrium. If this process is continued, a simple A-V junctional rhythm will result. However, if A-V junctional beat occurs later but still prior to antegrade activation of the A-V junction by the S-A node, each impulse will find conduction limited due to overlapping refractory periods, and there will be interference with the impulse progression in either direction. This failure of A-V conduction in either direction results in A-V dissociation, but it is a consequence of the physiologic refractoriness and not an organic block.[5] If, during the A-V dissociation, the atrial impulse reaches the A-V junction when it is not refractory, conduction to the ventricle will occur resulting in a ventricular capture beat.

Parasystolic rhythm results when there is repeti-

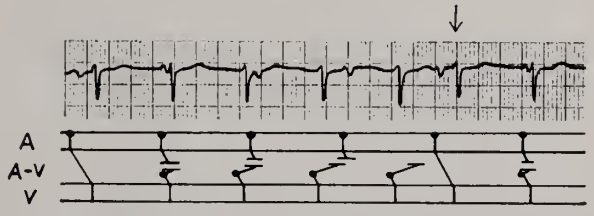


Fig. 8—Interference A-V dissociation results from an A-V junctional rhythm occurring at a slightly faster rate than the S-A nodal rhythm. Both S-A nodal and the A-V junctional rhythm interfere with the impulse propagation of the other by rendering conduction tissue refractory. If the atrial impulse occurs when the A-V junction is not refractory, the former will be conducted to the ventricle resulting in a ventricular capture beat (arrow). This proves that the A-V conduction system is intact. The primary disorder is an accelerated A-V junctional rhythm which is modified by the refractory period of the conduction tissue resulting in an A-V dissociation.

tive spontaneous impulse formation from an ectopic site occurring in competition with the dominant pacemaker. That the parasystolic impulse emerges only periodically is due to the refractoriness of the adjacent tissue. The concept of ventricular parasystole may be visualized by a situation in which a fixed rate artificial ventricular pacemaker has been placed in a patient with complete heart block, who has subsequently recovered normal A-V conduction (Figure 9). This situation fulfills the criteria of ventricular parasystole in that: (1) there is a constant discharge of ectopic impulses (artificial pacemaker) which are "protected" from the normal sinus beats, and (2) intervals between any two pacemaker-induced beats are multiples of the basic pacemaker interval. Many of the pacemaker impulses will fail to depolarize the ventricles because they occur during the ventricular refractory period. Those pacemaker impulses which by chance occur during the period of ventricular excitability will depolarize the ventricle and result in sporadic capture beats.

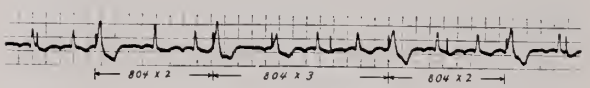


Fig. 9—An artificial ventricular pacemaker rhythm coexists with the patient's own rhythm. The artificial pacemaker acts as a ventricular parasystolic focus. Many pacemaker stimuli fail to capture the ventricle because of the refractoriness of the adjacent tissue. This represents an artificially created ventricular parasystolic rhythm. Artificial pacemaker discharge interval is 804 millisecond.



Fig. 10—A precordial monitor lead in a patient with an artificial demand pacemaker in the ventricle. The P waves are tall and simulate QRS complexes. The fact that the third pacemaker stimulus (arrow) is able to depolarize the ventricle indicates that the complex immediately preceding it could not be a QRS complex when one considers the role of the refractory period.

Understanding the role of the physiologic refractory period would avoid confusion in interpretation of the tracing taken from a patient with an artificial demand ventricular pacemaker as illustrated in Figure 10. In this tracing obtained from a monitor lead, the P waves are tall and were mistaken for QRS complexes. This resulted in the erroneous conclusion that a competitive rhythm was present and that the demand pacemaker was malfunctioning. However, careful attention to the third pacemaker beat indicates that for the ventricle to be depolarized consecutively at such a short interval would be in contradiction to normal electrophysiology. Hence, one of these two complexes has to be other than a QRS complex and actually is a distorted tall P wave.

Automaticity

Automaticity is another physiologic property of the specialized cardiac cells which often modifies a primary rhythm disorder. One may visualize automatic cells as physiologic demand pacemakers. Pacemaker cells are different from other myocardial cells in that they do not maintain constant resting potentials. Instead, the resting potential slowly and spontaneously drifts in the direction of depolarization (diastolic depolarization). When it reaches a given level known as the threshold potential, the cell develops action potential, thus acting as a pacemaker cell.[1] The S-A node normally governs the cardiac rate because it has the steepest slope of diastolic depolarization and reaches threshold potential earliest of all other potential cardiac pacemakers (Figure 1b). The subsidiary pacemakers in the A-V junction and ventricle also undergo diastolic depolarization but at a slower rate. If atrial impulse fails to reach the A-V junction before diastolic depolarization of the A-V junctional tissue reaches threshold potential, the junctional tissue depolarizes spontaneously, resulting in an escape beat. This response is similar to that of a demand pacemaker.

An example of a complicated consequence of this "demand pacemaker" in the A-V junction is demonstrated in Figure 11. In this patient, there is first degree A-V block and the atria are no

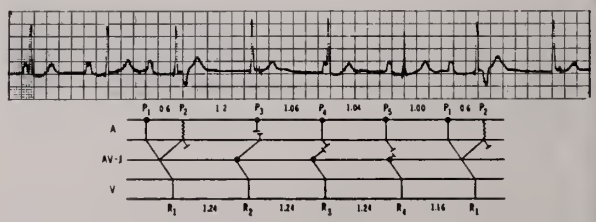


Fig. 11—A prolonged PR interval allows re-entry of the impulse from the A-V junction to the atrium and resets the sinus rhythm. This in turn creates a long pause and the "demand pacemaker" in the A-V junction escapes for the succeeding three beats. Because of the physiologic refractory period, momentary AV dissociation results. The primary disorder is a 1° AV block which is modified by automaticity and refractory period of the conduction tissue resulting in an A-V junctional escape and A-V dissociation.

longer refractory by the time ventricular depolarization occurs. This allows atrial re-entry of the impulse from the A-V junction and resets the S-A nodal pacemaker. The resulting pause is of sufficient duration for the "demand pacemaker" in the A-V junction to escape. The next two atrial impulses (P_3 and P_4) occur during the refractory period of the junctional tissue and A-V junctional rhythm continues. The next atrial beat (P_5) might have been conducted to the ventricle but, due to the first degree A-V block, the delay in conduction results in another junctional escape beat. Finally, the antegrade atrial impulse (P_1) reaches the A-V junction at a time when the junctional tissue is excitable and disrupts the A-V dissociation. In this example, first degree A-V block and sinus bradycardia are actually the primary disorders and the additional phenomena of retrograde conduction to the atrium, resetting of the S-A nodal rhythm, A-V junctional escape, and interference A-V dissociation occur as physiological responses. Manifestation of the demand pacemaker in the A-V junction is responsible for the genesis of transient interference A-V dissociation following a pause induced by a VPB or nonconducted APB.[3] This concept of the demand pacemaker is clearly illustrated in Figure 12, where the role of the subsidiary pacemaker is replaced by an actual artificial demand pacemaker.

An appreciation of the effect of automaticity also aids in the understanding of interference A-V dissociation with 2:1 A-V block as illustrated in Figure 13. Although this appears to be a complicated arrhythmia, 2:1 A-V block with A-V dissociation is essentially a manifestation of a "demand pacemaker" in the A-V junctional tissue and the physiologic refractory period of the conduction system. When one-half of the S-A nodal rate drops below the intrinsic rate of the A-V junctional pacemaker in a patient with 2:1 A-V block, the A-V junctional pacemaker will escape. Because of the physiologic refractory period interference A-V dissociation results.

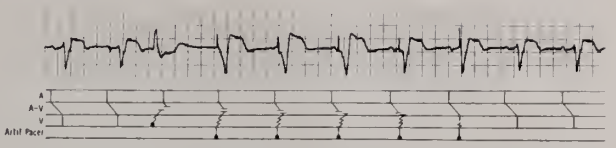


Fig. 12—This patient has an artificial demand pacemaker placed in the right ventricle. A full compensatory pause induced by a VPB (the third QRS) allows this demand pacemaker to take over the ventricular rhythm for the subsequent five beats. During this period, the atria are under the control of the uninterrupted S-A nodal pacemaker whose rate is slightly faster than the artificial pacemaker rate. Because of the physiologic refractory period of the A-V junctional tissue, interference A-V dissociation results.

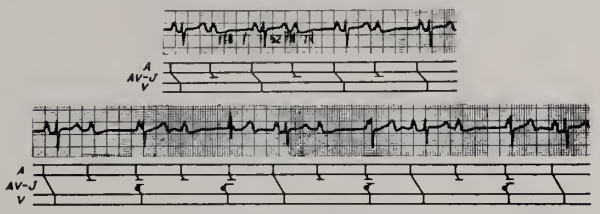


Fig. 13—A 2:1 A-V block is evident in the upper tracing. A moment later (lower tracing), the sinus rate is slightly slower and one half of sinus rate (41/min.) drops slightly below the intrinsic rate of the A-V junctional pacemaker (43/min). This allows the A-V junctional pacemaker to escape, but, because of physiologic refractoriness, A-V dissociation results.

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It's the Law

The following case description is one that may well be of far reaching importance in medical malpractice cases. It is felt likely that courts in other states will follow the precedent of the Washington State Supreme Court. This represents a very basic change in previously held legal precedence.

Ophthalmologists Held Duty-Bound to Routinely Test for Glaucoma

The case involved a 32-year-old patient who suffered from primary open angle glaucoma. She had lost her peripheral vision and her central vision was reduced. She had been seen by ophthalmologists but occular tension was not obtained. After approximately five years of symptoms she was seen by another ophthalmologist who made the diagnosis of glaucoma. The patient and her consulting lawyers brought suit against the original ophthalmologist alleging that she sustained severe and permanent damage to her eyes as a result of the ophthalmologist's negligence in not determining her occular tension.

Medical experts for both sides agreed that in the absence of symptoms of glaucoma, the standard of the profession did not require routine pressure testing in patients under the age of 40.

The court ruled that under the facts of this case, reasonable prudence requires the timely giving of the pressure test. "We therefore hold as a matter of law that the reasonable standard that should have been followed under the facts of this case was the timely giving of this simple harmless pressure test and that in failing to do so the ophthalmologists were negligent."

In the Washington Supreme Court, a three judge panel handed down an opinion that the liability should have been posed on the basis of strict liability without fault or negligence on the ground that negligence implied moral blame. In this case the ophthalmologists acted reasonably and according to the standards of their profession. The patient, however, was awarded damages.

In determining who should bear the loss of their failure to administer the glaucoma test, the judges pointed out that the physicians, because of their malpractice insurance, were financially better able to bear the loss than was the patient.

Comment: The Washington State Supreme Court has departed from the well established general rule which requires physicians to conform to the standard of practice established by the medical profession. The court ruled that ophthalmologists, at least those in the state of Washington, must test for glaucoma in all examinations regardless of the patient's age.

Theodore A. Peterson, M.D.
Minneapolis, Minnesota

Helling v. Carey (Sup. Ct. Wash., Docket No. 42775, Mar. 14, 1974). Reference: Darrell L. Havener, Esq., Watson, Ess, Marshall, and Enggas, 1006 Grand Ave. Kansas City, Mo. 64106. The Citation 29:2, May 1, 1974.

Cover Photo

"Sultan's Library"

On the cover is a photograph of the Sultan's Library in the Topkapi Museum grounds in Istanbul taken by Reuben Berman, editor emeritus of MINNESOTA MEDICINE, early in January of this year. Kodachrome 25 slide film was used with a 50 mm lens in a TOPCON Camera. Exposure was determined by light meter at f 5.6 at 1/30 sec. The photographic problem was to show the surrounding and background details without excessively overexposing the sunlit marble building.

An 8 x 10 enlargement will hang with the Marvin Sukov collection in the University of Wisconsin Library, Madison.

Grand Rounds

Hepatorenal Syndrome

WILLIAM SHIMP, M.D.*

THE TERM "Hepatorenal Syndrome" (HRS) usually refers to the *functional* renal failure of advanced Laennec's cirrhosis, but the term means different things to different people. On the wards and throughout the medical literature, confusion has been generated by applying this single term to a variety of meanings.

Definition

For the purpose of this discussion, I define HRS as the renal failure that occurs with decompensated liver disease and, in most cases, with refractory ascites. Azotemia and oliguria occur without apparent cause, there being no preexisting renal disease and usually no precipitating event. Progressive dilutional hyponatremia commonly occurs. The urine sediment is normal or shows only minor changes. The amount of urinary sodium excreted is characteristically low, the specific gravity high, and the urine/plasma osmolality ratio greater than unity—this reflecting preservation of tubular function. No consistent or significant changes in renal histology have been reported. The prognosis is grave, but improvement (with survival) may sometimes occur.[1,2]

Pseudo-Hepatorenal States

Less specific use of the term "hepatorenal syndrome" encompasses all other conditions wherein renal and liper failures occur simultaneously, and these may be more properly termed "pseudo-hepatorenal" syndromes.[1] Generalized disorders such as infections (leptospirosis, yellow fever, Reye's syndrome), circulatory disturbances (shock, congestive heart failure), genetic aberrations (polycystic disease, sickle cell anemia), collagen vascular disease (SLE, periarteritis nodosa), and disorders of unknown etiology (toxemia, amyloidosis, sarcoidosis, Waterhouse-Friderichsen syndrome, hyperthermia) may affect both organs simultaneously, as may toxins (carbon tetrachloride, copper sulfate, chromium, toadstool toxins, methoxyfluorane, tetracyclines, streptomycin, sulfonamides, and iproniazid). Also, neoplasms may involve both organs at the same time and produce dysfunction in both. These pseudo-hepatorenal syndromes are usually easy to differentiate from the true HRS by recognition of the precipitating event or by characteristic clinical, laboratory, or functional features of the hepatic and/or renal lesions.

Underlying Renal Disease

Renal failure may also occur in the cirrhotic for reasons unrelated to the liver disease, and the etiology should be just as fully investigated in the cirrhotic as in the non-cirrhotic. Renal failure should never be regarded as being secondary to liver disease, and the diagnosis of HRS never made, until all other etiologies have been ruled out. Thus, the classic prerenal, renal, and postrenal cause for renal failure must be differentiated.[3-5] Shear, et al., studied fifteen patients dying with cirrhosis and renal failure diagnosed as having HRS, and found that half of the patients had features more characteristic of acute tubular necrosis, and several others had preexisting renal disease: less than one-third had the clinical pattern of the true HRS.[6]

Pathogenesis

Strong evidence points to the *functional* nature of the renal failure in HRS. As noted above, biopsied or necropsied kidneys are usually histologically normal. Also, HRS kidneys have been transplanted into non-cirrhotic patients with development of excellent renal function.[7] Conversely, liver transplantation performed on azotemic cir-

*Medical Resident, Hennepin County Medical Center, Minneapolis, Minnesota.

Edited by: Arthur Leonard, M.D., Coordinator, Medical Education and Attending Physician, Department of Medicine, Hennepin County Medical Center.

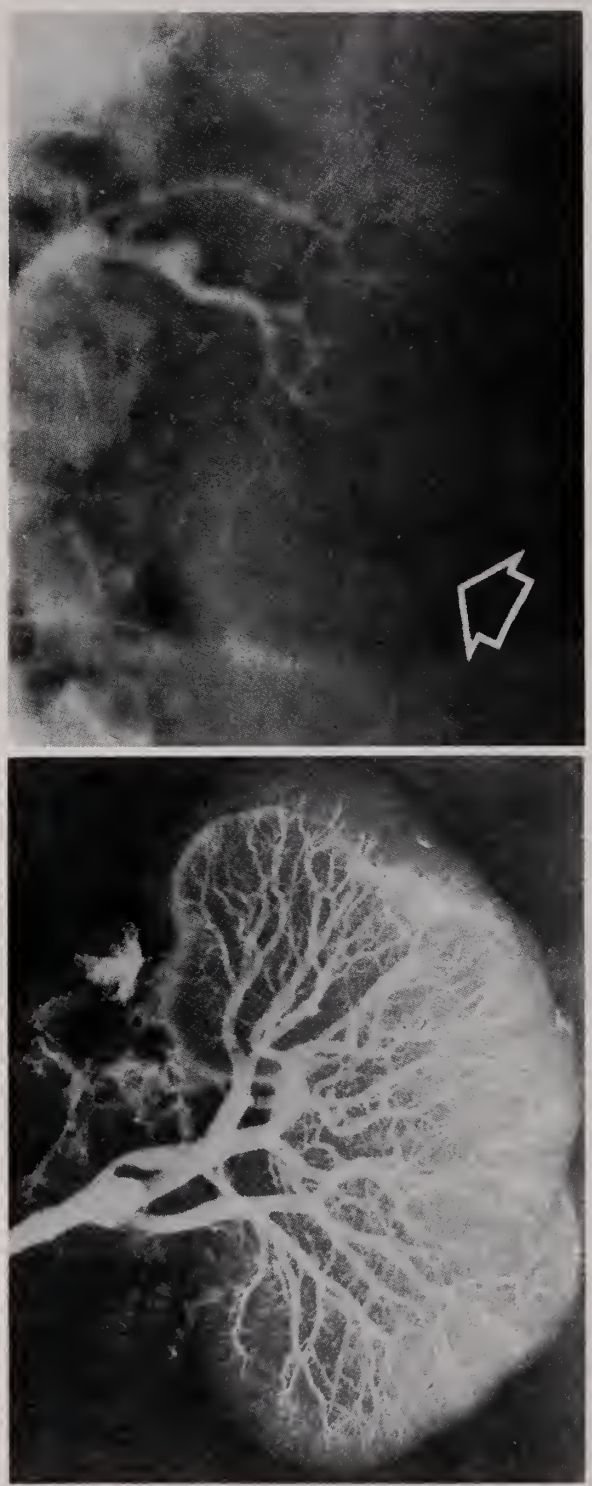


Fig. 1—(Top) selective renal arteriogram performed in a patient with cirrhosis and renal failure. The distal renal vasculature is not recognizable, and no distinct cortical nephrogram is present. The arrow indicates the edge of the kidney. (Bottom), renal arteriogram performed post-mortem on the same kidney. The entire renal vasculature to the periphery of the cortex is well-visualized. The vascular attenuation and tortuosity is no longer present.[9]

rhotics has resulted in return of renal function.[8] Epstein has demonstrated angiographically that reversal of the characteristic abnormality, which consists of intense constriction of the vasculature supplying the renal cortex, occurs post mortem (Figure 1). That the disturbance is functional, therefore, means that the kidney is essentially normal in HRS, and that renal dysfunction is the result of the interplay of abnormal external forces.

It is a fair statement to say that the etiology of HRS remains unknown, although a good deal of recent information has been gathered that further defines and quantitates the renal defects in HRS. Many pathogenetic mechanisms for the syndrome have been proposed, and several of them merit further discussion.

Decreased Plasma Volume

Since ascites (and often edema) is almost invariably present in HRS, it is obvious that these patients are volume-overloaded. However, since ascites and edema accumulation occurs at the expense of plasma volume, intravascular volume depletion has been postulated as a cause of HRS, presumably acting as a prerenal factor. This hypothesis has gained support from the observation that renal failure in cirrhotics is frequently precipitated following a gastrointestinal hemorrhage, paracentesis, or vigorous efforts at diuresis—events that further deplete intravascular volume. However, plasma volume in cirrhotics with HRS has been demonstrated by most investigators to be at least normal and usually increased, sometimes 20 to 25 percent above normal controls.[10]

A modification of the above theory proposes a decrease in the *effective* plasma volume; that is, the measured increase in plasma volume may represent plasma pooled in a dilated, hypertensive splanchnic bed, and the arterial or "effective" plasma volume actually involved in organ perfusion may be decreased. This thesis is supported by the work of Tristani and Conn, who, in 1967, reported transient therapeutic success in improving renal function in HRS following volume expansion with dextran.[11] The patients they studied could be grouped into two classes: those with a decreased cardiac index and a lower plasma volume (low-output HRS), and those with an increased cardiac index and a higher plasma volume (high-output HRS). Though measured plasma volume was normal or elevated in both groups,

they found that the first group responded much more dramatically than the second to volume expansion. The cardiac index rose, the systemic and renal vascular resistance declined from elevated levels, and the proportion of cardiac output going to the kidneys increased. In addition, there occurred an accompanying increase in urine flow and sodium excretion. Unfortunately, however, the improved renal function was transient and most patients returned to their original status after the infusion was stopped. Moreover, though the authors considered it helpful to distinguish between the two groups with respect to predicting which patients might best respond to volume expansion, they admitted that this distinction could not usually be made clinically, and measurement of plasma volume and cardiac output was necessary.

Reynolds, et al. tried volume expansion in sixteen patients with HRS, with no effort being made to differentiate between low- and high-output groups.[12] Although nine responded with increased renal function, eight of these died. Four of the sixteen patients died of variceal bleeding during or immediately following volume expansion. This led to the speculation that the increase in plasma volume had increased collateral flow to the point of causing variceal rupture. They concluded plasma expansion was of no long-term benefit and that it might, in fact, be dangerous.

Renal Vasoconstriction and Intrarenal Shunting

Early studies of HRS demonstrated a reduction in both renal plasma flow and glomerular filtration rate, the latter being more significantly reduced than the former. This observation, along with a noted decrease in para-amino hippurate (PAH) extraction (the renal medulla does not extract PAH), suggested shunting of an already diminished renal plasma flow away from the cortex to the medulla.[13,14] The low renal plasma flow rate was felt to be secondary to renal vasoconstriction, as was suggested by the measurement of an increased renal resistance to blood flow. Therefore, an abnormally small percentage of the cardiac output was being delivered to the kidneys.

Arteriography visually confirmed the conclusions of earlier studies. As was alluded to previously, a marked constriction of the interlobar and proximal arcuate arteries has been demonstrated angiographically.[9] This is not unlike the x-ray findings induced by infusion of norepinephrine directly into the renal arteries of normal kidneys.[15] Consequently, efforts to reverse the lesion with infusion of alpha-adrenergic blocking agents have been made, but the results have been inconsistent and discouraging.[9,16] Efforts to identify the humoral or neural factor responsible for this vasoconstriction have also been unsuccessful, although most investigators believe that a substance produced by the diseased liver, or not detoxified by it, is responsible.

^{133}Xenon washout studies have provided interesting and confirmatory evidence for renal vasoconstriction and intrarenal shunting.[9,15,17] The technique involves injecting ^{133}Xe into the renal artery and following its disappearance from the kidney with an external counting device. The resultant curve can be resolved into three exponentials, each defining a slope associated with blood flow through a different region of the kidney. The first (or most rapid) component represents clearance of the inert gas from the outer cortex; the second, clearance from the juxtamedullary region and outer medulla; and the third, from the inner medulla. Sixty to ninety percent of the

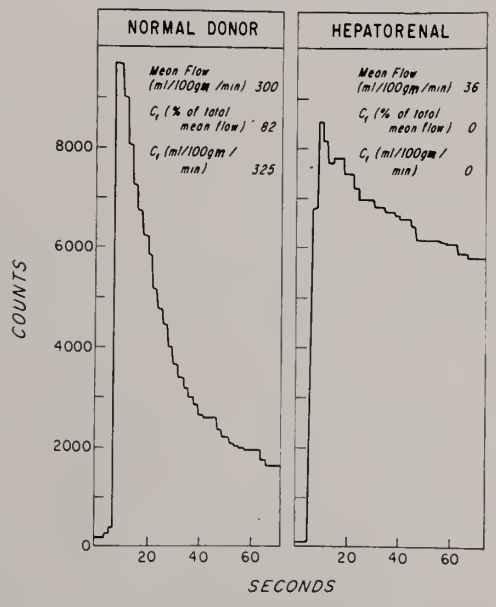


Fig. 2—On the left, xenon washout curve in a normal transplant donor. C-1 is the rapid cortical component and is represented by the steep-sloped portion of the curve. Eighty-two percent of the isotope is in C-1. On the right, a washout curve in a patient with hepatorenal syndrome. There is no cortical component present, as indicated by the absence of a steep slope. All of the isotope is in the renal medulla (C-2 and C-3).[9]

isotope is normally in the first (rapid) component; in HRS, the percentage is 0-30, indicating poor flow to the renal cortex. Graphically, this is represented by loss of the normal steep slope of the washout curve (Figure 2). HRS is certainly not the only condition in which this occurs. Acute tubular necrosis secondary to shock, renal failure from nephrotoxins, acute glomerlonephritis, and severe renal allograft rejection all show similar angiographic and isotope washout patterns, indicating preferential cortical ischemia. However, when the "stability" or regularity of the disappearance of isotope is assessed, it is found that HRS differs from all other forms of acute renal failure. The HRS disappearance curve is irregular and variable, implying considerable hemodynamic variability from minute to minute (Figure 3).

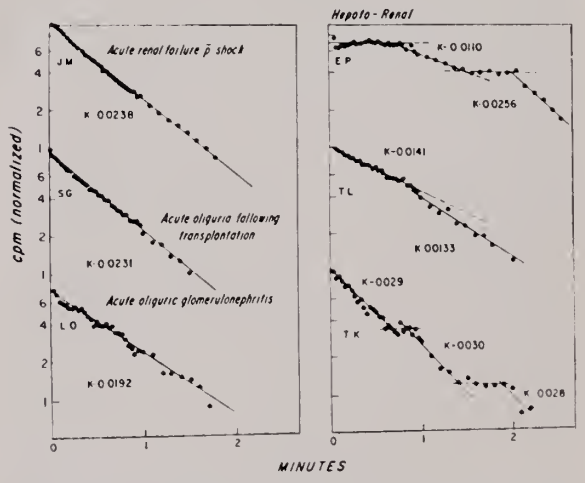


Fig. 3—Normalized semilogarithmic xenon disappearance curves. On the left, the regularity (linear nature) of xenon disappearance is evident in acute renal failure secondary to shock, transplantation, and glomerulonephritis. On the right, HRS patients demonstrate extreme variability of isotope disappearance, suggesting the presence of vasomotor instability.[9]

Epstein and Hollenberg have further correlated these findings with clinical assessment of the patient and measurement of renal function.[9] They studied 15 biopsy-proven cirrhotics and compared them to normal controls, further subdividing them into groups with normal renal function, abnormal renal function but without azotemia, azotemic, and oliguric (HRS). They demonstrated that as creatinine clearance declines, so also does the percentage of isotope present in the rapid flow compartment (Figure 4). They concluded from this that renal function in cirrhosis represents a continuum in which the alterations in renal perfusion in non-azotemic cirrhotics are similar to, but milder than, those seen in HRS. Their work suggests an explanation for the ease with which the cirrhotic can be "tipped into" renal failure following even minor fluid shifts secondary to bleeding, paracentesis, or administration of diuretics.

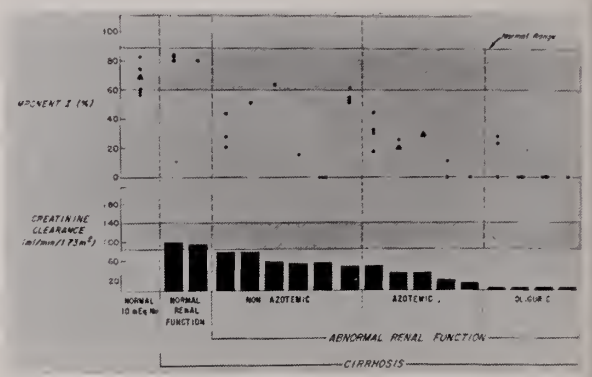


Fig. 4—Relationship between the percentage of total renal blood flow in the cortical component (C-1) and creatinine clearance in normal and cirrhotic patients on a low sodium diet. There is a decreasing percentage of blood flow in the cortical component as creatinine clearance decreases.[9]

Increased Abdominal and Renal Vein Pressure

HRS is almost invariably associated with ascites. Although the presence of ascites may be viewed as the result of the severe sodium retention and inability to excrete a free water load characteristic of the decompensated cirrhotic state, the reverse association wherein ascites might contribute to HRS has been studied. It has been shown in animals and man that increased abdominal pressure (e.g., ascites, abdominal compression by pneumatic girdle, prolonged Valsalva) will decrease glomerular filtration rate, renal plasma flow, urine volume, and sodium excretion, and will increase inferior vena cava, portal, and renal venous pressure.[18] This is not unlike the hemodynamic and urinary changes seen in HRS. Naturally, the relief in intra-abdominal pressure by various means has been studied as a potential therapeutic maneuver in HRS.

Early studies showed that an increase in urine flow and sodium excretion could be effected by lying the cirrhotic on his side, or by placing him prone on a Strycker frame such that the abdomen received no external pressure.[18] Presumably, removal of IVC compression increased effective plasma volume by promoting venous return. More recently, it has been shown that paracentesis may

actually reverse the hemodynamic changes seen in low-output HRS—namely, the decreased cardiac output and stroke volume, and the increased peripheral vascular resistance and IVC pressure.[19-21] Knauer found that paracentesis of 750-1,000 cc. improved these parameters, and concluded that small paracenteses might be useful hemodynamically[20] (Figure 5). Larger paracenteses were noted to cause a return to the original measurements, presumably secondary to volume depletion. However, none of his cirrhotic patients were actually in HRS, and no data on renal function were generated; thus, it can only be inferred that such a maneuver might be useful in the treatment of HRS.

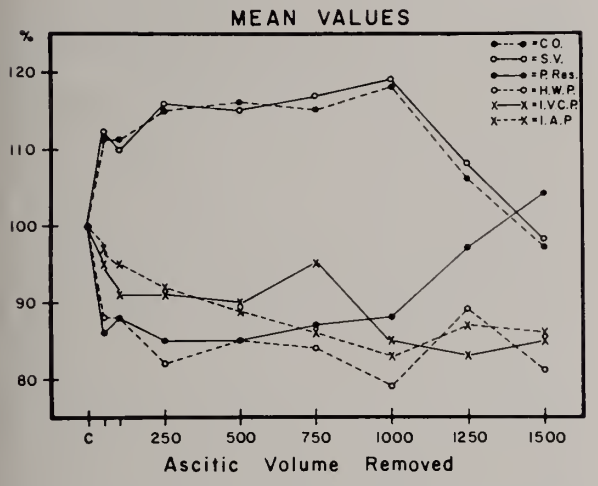


Fig. 5—Composite data graph showing the relationship between volume of paracentesis and cardiac output (C.O.), stroke volume (S.V.), peripheral resistance (P. Res.), hepatic wedge pressure (H.W.P.) inferior vena cava pressure (I.V.C.P.), and intra-abdominal pressure (I.A.P.).[20]

Increased portal, vena caval, and renal venous pressure is an almost invariable finding in advanced cirrhosis. In 1964, Baldus showed the renal vein pressure to be higher in ascitic cirrhotics in renal failure than in those with intact renal function.[22] Clinically and experimentally it has been demonstrated that elevated renal venous pressure decreases GFR and sodium excretion. Because there is a direct and expected correlation between renal venous and IVC pressures, Mullane in 1967 studied the relationship between IVC pressure and HRS.[23] He found this pressure to be elevated in 43 of 45 cirrhotics, and in all nine patients with HRS. Interestingly, the pressure increase could not be reliably correlated with the presence of ascites, and therefore, could not always be attributable to transmission of ascitic pressure to the intra-abdominal veins. He postulated that cellular regeneration and fibrosis in the cirrhotic liver might distort the caudate lobe, with consequent narrowing and compression of the nearby IVC. This explanation was correlated with impressive anatomic data. He found the caudate lobe to be significantly thickened and extended into the IVC, and the distance between the caudate and right lobes of the liver was significantly diminished. Further, he correlated the increased IVC pressure with abnormalities of renal function, and concluded that IVC compression might be responsible for a yet undetermined part of HRS. Redistribution of renal blood flow in response to renal venous hypertension might reduce glomerular perfusion, he said, and increase medullary flow secondary to induced intrarenal shunting.

Hepatic Failure

As with hepatic encephalopathy, HRS has been blamed on the presence of toxins or other humoral factors that are either elaborated by a failing liver or not metabolized by it. Experimentally, the survival and functional activity of rat kidneys was prolonged when perfused in combination with the liver, suggesting that normal liver function may be a prerequisite for viability of the kidney.[24] The most obvious potential toxin is bile, which can readily be identified in the HRS kidney as an intense staining of the epithelium of Bowman's capsule and proximal convoluted tubules with pigment granules. Vacuolization and degeneration of tubular epithelium, especially near bile casts, can be found. However, this lesion occurs in cholestasis of all types, and is often associated with normal renal function.

Most HRS patients have hepatic encephalopathy, and the question of whether the same toxin is producing brain and kidney dysfunction has been raised. Ammonia has been studied as one such potential toxin. Though direct infusions of ammonia into the renal artery cause prompt reduction of GFR,[25] efforts to relate ammonia level to renal dysfunction have not been successful and proof of an etiological relationship has not been offered.

Fischer, et al., suggested the presence of false neurotransmitters, inert amines might replace active amines such as norepinephrine and dopamine

at central and peripheral nerve endings, thereby opening peripheral vascular shunts and leading to perfusion of nonessential areas such as muscle and skin, at the expense of the renal circulation.[26] Within the kidney, opening at such shunts could divert blood away from the cortex. They pointed to presumptive evidence of peripheral norepinephrine depletion by noting failure of response to tyramine infusion in HRS. Thus, they treated high output HRS with infusions of metaraminol and L-dopa, hoping to close these postulated shunts and increase cortical perfusion. They were able to temporarily improve the abnormal renal function and hemodynamics, but return to baseline dysfunction occurred when the infusion was stopped, and no significant change in mortality occurred. Bennett, et al. in a preliminary report, confirmed such improvement with ^{133}Xe washout and arteriography studies following infusion of subpressor doses of dopamine in seven out of eight HRS patients. Moreover, they claimed a permanent return to normal renal function in two patients temporally related to the infusion.[27]

In contrast to vasopressor depletion, vasopressor excess has also been proposed as a cause for HRS. Pointing to renal and peripheral vasoconstriction as compatible with pressor excess, some investigators have tried alpha-adrenergic blockade with phentolamine and dibenzyline. Results have been discouraging, but not surprising because of the normal concentrations of catecholamines, 5-HIAA, and 5-hydroxy-tryptamine found in the urine and serum of HRS patients.[16]

A catecholamine-related therapeutic effort was proposed by Kew in 1972.[28] Octapressin, a synthetic analog of vasopressin, was suggested as a theoretically ideal agent for treatment of HRS in that it increases systemic resistance, dilates the renal vasculature, and lowers portal pressure. Experimentally, however, only conflicting and inconclusive data could be generated.

The renin-angiotensin-aldosterone system has recently been implicated in the genesis of HRS. Aldosterone excess has been shown to occur in virtually every edematous state, including cirrhosis of the liver (with or without HRS).[29] Plasma renin levels have shown a direct correlation with the degree of renal dysfunction in cirrhosis.[30] Though almost all cirrhotics have high renin levels, those with renal compromise have significantly higher levels. This may be due to decreased arteriolar perfusion resulting from intrarenal hemodynamic alterations or decreased effective blood volume, which in turn causes a decreased GFR and decreased renal plasma flow. Failure of hepatic metabolism of renin might also contribute to this phenomenon.

Interestingly, plasma renin substrate (angiotensinogen) is markedly decreased in azotemic and non-azotemic cirrhotics.[8,30,31] This is not surprising in that the liver is the major source of the substrate. In reporting reversal of azotemia in cirrhotics following orthotopic liver transplantation, Iwatsuki, et al. showed that a striking increase in renin substrate levels occurred promptly after surgery, accompanied by a fall in renin levels —both of which were followed by an increase in renal function.[8] Also, in those patients who respond to metaraminol infusions, similar enzyme and substrate changes have been reported.[26] Assuming the cirrhotic to be incapable of generating adequate amounts of angiotensin, therefore, some investigators have tried angiotensin infusion in HRS. However, there are technical difficulties involved in performing the infusion (larger and larger doses required to produce the same pressor response), and the results have been variable. A variation on the same theme is to infuse renin substrate, and this was attempted this year at the University of Minnesota. Fresh frozen plasma from a pregnant donor (therefore, high in renin substrate) was given to a woman with HRS, with reported complete recovery and ultimate discharge from the hospital.[32]

Treatment

As was mentioned above, the level of renal dysfunction in cirrhosis tends to occur as a continuum, and it is reasonable to assume, until proven otherwise, that all cirrhotics have some degree of renal impairment. This, coupled with the observation that cirrhotics can be "tipped into" renal failure with even slight manipulation of their fluid spaces, should lead one to avoid therapeutic efforts that could worsen renal function, and to vigorously support the intravascular space in times of blood loss and hypotension. Excessive efforts at diuresis, large-volume paracenteses, and severe fluid restriction all carry considerable potential for harm, and should be avoided if possible.

The routine supportive measures such as high carbohydrate-low protein diet, sodium and fluid

restriction, oral or rectal neomycin, bedrest, and aggressive treatment of concurrent infections should be undertaken. Beyond this point, one may argue convincingly for a policy of therapeutic nihilism, citing the lack of favorable influence of any described therapeutic modality on the final outcome of the syndrome. After all, it may be argued, the prognosis of HRS is that of the liver and not of the kidney, so why should therapy be directed at the kidney? Indeed, although renal failure is present, greater degrees of failure in the non-cirrhotic are compatible not only with life, but with an active, productive existence. While it is possible that the cirrhotic may be more sensitive to a given degree of azotemia than the non-cirrhotic, the question must still be raised whether death in HRS is related to renal failure at all, or whether the renal failure is simply an indicator of further progression of the underlying hepatic dysfunction.[33] HRS patients appear to die *in* renal failure and not *of* renal failure.

Nonetheless, the Table lists the therapeutic measures that have been, and may be, tried. Claims of success have been made for all, the usual end point being *temporary* improvement in renal function, with no observable effect on the dire mortality statistics. However, some claims of reversal of HRS as a result of the therapy rendered have also been made. Given that some patients will spontaneously recover, it is difficult to judge whether therapy had any influence on the recovery. To date, no controlled study on the effectiveness of therapy has been done.

Terminal Events

The cause of death in HRS is no different from that in non-azotemic cirrhosis: gastrointestinal hemorrhage, hepatic coma, infection, refractory hypotension, etc. Terminally in HRS, the laboratory picture may change. Though severe oliguria persists, sodium excretion increases, the specific gravity falls, abnormal cellular elements appear in the urine, and the urine/plasma osmolality ration may fall below unity.[17] This most likely reflects loss of the previously intact tubular function, and almost always occurs in association with severe hypotension. Thus, terminally, the HRS may resemble acute tubular necrosis.

TABLE
Possible Therapeutic Measures

1. **Volume expansion**
   - a) Ascitic fluid reinfusion[34]
   - b) Ascitic fluid reinfusion plus furosemide[35]
   - c) Dextran[11] } May be more effective
   - d) Plasma, albumin[12,36] } in low-output HRS
2. **Catecholamine-related agents**
   - a) Metaraminol[26,37,38] } May be more effective
   - b) L-dopa[26] } in high-output HRS
   - c) Dopamine[27]
   - d) Dibenzyline[9,16]
3. **Hormonal**
   - a) Angiotensin[14]
   - b) Renin substrate (angiotensinogen)[32]
   - c) Octapressin[28]
   - d) Steroids[1]
4. **Dialysis**[39,40]
5. **Surgical**
   - a) Paracentesis (750-1,000 cc)[20]
   - b) Portacaval anastomosis[1,41,42,43]
   - c) Baboon liver hemoperfusion[39]
   - d) Liver transplantation[8]

Conclusion

The hepatorenal syndrome usually represents a terminal development in the progression of severe hepatic decompensation. Though functional changes in the kidney are now well described, the exact etiology eludes definition. There appears to be little the clinician can do to alter the outcome, though efforts at doing so may, on occasion, be rewarded. Controlled clinical studies on the effectiveness of current therapies are needed.

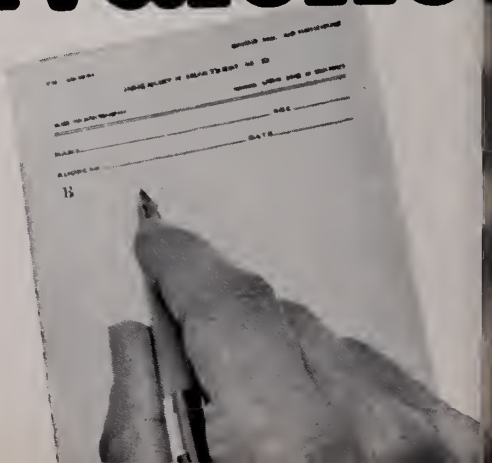
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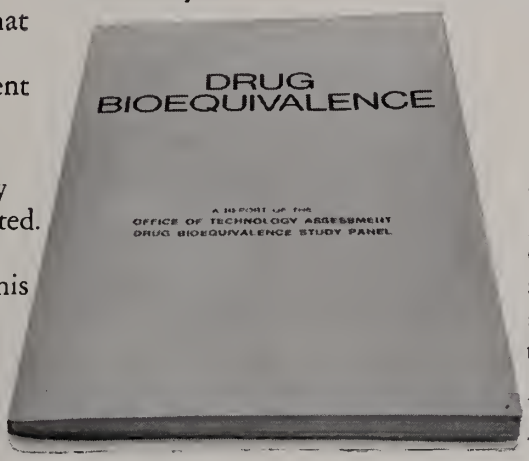
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Definitely not, unless bio- valence tests and other quality rance checks had been conducted. pharmaceutical industry and y scientists have maintained this ion for years, but others have tioned it. Now the Office of nology Assessment of the gress of the United States has rted on the issue in its Drug quivalence Study.*

Here are a few definitive state- ts in the O.T.A. report:

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"While these therapeutic failures resulting from problems of bioavailability were recognized and well documented, it is entirely possible that other therapeutic failures and/or instances of toxicity that had a similar basis have escaped attention."

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Psychiatry

Differentiating the Psychotic Child from the Mentally Retarded Child

ROBERT H. OLIN, M.D.*

PHYSICIANS ARE becoming increasingly aware that many children diagnosed as mentally retarded are, in fact, psychotic. To add to that awareness, this paper suggests that a criterion exists which will help the physician to diagnose these children more accurately.

Before examining this criterion, I'll make some summarizing statements about the psychopathology of the psychotic child and of the mentally retarded child.

Psychopathology of the Psychotic Child and the Mentally Retarded Child

The primary psychopathology in childhood psychosis is in the child's identity. He lacks a feeling of identity and develops a deep depression which he cannot recognize.

He is depressed because he lacked love or feels he lost his mother before he could comprehend this lack of love or this loss. So he experienced her loss as a loss of himself; at his young age, he sees his mother inseparably as the main part of himself that exists.

A look at the specific identity problems of the psychotic (either autistic or schizophrenic) child and the mentally retarded child might be helpful.

The autistic child's identity problem is one of feeling so small and insignificant that he hardly exists. So he defends against feelings of nonexistence by using all his strength and ability to try to be a shell of indestructible power. He hides his real self in his shell. He identifies with primitive thoughts from the world of infancy since these represent to the infant things of great permanence. Therefore, such a child may identify with a car, a sidewalk, or a light switch in his bedroom. He attempts to establish an omnipotent identity of power and indestructibility. He believes that all his needs are at his beck and call or have already been fulfilled. He acts as if he is without needs.

*Hopkins, Minnesota.

A schizophrenic child, on the other hand, feels his identity is very scattered and diffused—like mist in the air. He is afraid that if people really discover him, they will find that he doesn't exist and hence they will confirm his own feelings that he does not exist. He therefore attempts in his scatteredness to identify with almost everything in his environment—as if to become omnipotently everything. When a parent or a therapist attempts to get a clear picture of what he is saying or doing, the child evades him by becoming even more scattered. Again, he fears that he will be clearly seen or defined.

The organically retarded child may be psychopathic in addition to being retarded. The problems usually center around the child's awareness that his intelligence is low. This awareness is part of his identity and is realistic.

The retarded child may be very unhappy about his identity and may punish himself with guilt for his low functioning. He may dwell on his feelings of inferiority or he may constantly strive to function far beyond his abilities. Either action produces intense feelings of dissatisfaction in the child.

The retarded child is an open child and can discuss these feelings of dissatisfaction with much emotion.

Criteria for Differential Diagnosis of Childhood Psychosis and Mental Retardation

To diagnose correctly the autistic child, the schizophrenic child, and the mentally retarded child, the therapist must examine the child clinically, observe the family dynamics, and take a careful history of the child. Let's look at each of these processes for each of the groups of children.

Autistic Child

Clinical Observations

The autistic child tends to be an isolated child

—as if he lives in a shell. He will have some of the following symptoms: difficulty mixing with other children; a standoffish manner; a resistance to learning; and a resistance to changes in his routine. He will act as if he were deaf. He will not be cuddly and he will make no eye contacts. He will sustain odd play and have an inappropriate attachment to objects, which he frequently spins. He will laugh and giggle inappropriately and indicate his needs by gestures. He has no real fear of real dangers. He hides his extreme sensitivity and his identity in an air of indifference. Paranoid delusions underlie some of these symptoms. Hallucinations are usually not present in the autistic child, although they may be present in some of the less severely autistic children, or during the recovery stage of a child in therapy.

Family Dynamics

The parents of the autistic child frequently appear very normal and adaptable on the surface. Below the surface, however, they may be very stubborn and feel omnipotent.

In the family, one parent influences the combined parental attitude toward the child, and often completely rejects the child and may physically abuse the child. Yet the parents tend to stick together and support each other. Thus they hide any abuse. Also, they stick together by taking turns giving in to each other. Their contact with the child has approach and rejection intermixed.

When real disagreements come into the open the parents may tend to be explosive. This may result in a split in the marriage.

Frequently the child was born at a time when no children were wanted, or when the mother was depressed, or when the marriage was in trouble.

The parents will often take an "approach-rejection" route in seeking help for their child. Thus they may seek educational help in place of psychiatric treatment. This is an attempt to help the child, (an approach), but it ignores the child's critical need for treatment (a rejection).

History

Some of our autistic children have histories of having been physically immobilized during the first year of their lives. This immobility prevents the child from using his body to make contact with his environment and prevents him from learning about his body and from experiencing its realness.

Parental approach-rejection behavior may also have had an immobilizing effect on the child. Parently lack of stimulation or of over stimulation is common. The child thus early withdraws from his body and goes into his mind. He develops a negative body image of himself and disassociates himself from his body's perceptual motor system.

Later body experiences have been held to a minimum by ritualistic behaviors and this behavior prevents new experiences from countering the negative body image.

His mind seems to develop as an observer of his body rather than as a participant with his body. The child also becomes an observer of life rather than a participant in life.

This observer-participant split is the psychotic split of the autistic child: his mind is split from his body.

Case Report

A four-year-old autistic child was referred by the child's physician after he learned about the symptoms of autism. (Prior to the referral, the child had been seen by a psychologist who, after he had tested the child, diagnosed the child erroneously as retarded). Shortly after the child was born, the physician discovered, a rectal insertion of a thermometer had ruptured the child's colon. A year of being forced to lie on his back with an open colostomy followed.

An approach-rejection pattern in the parents began at that time. They developed intense feelings of empathy for and desires to save the child—who, over a prolonged period, came close to dying. But the parents also, as the problem wore on, wished the child would die. This wish was rationalized into the idea that the child (and they) would be better off if he did die.

Confused, the parents became unable emotionally to differentiate their real heroic labors to care for and save the child (an approach) from their wishes to kill the child (a rejection).

A continued approach-rejection relationship with the child continued until the child was brought to our clinic for treatment.

The autism was the child's method of dealing with this approach-rejection attitude of the parents (autism thus is an anti approach-rejection posture). The child was confused as to whether the parents' contacts with him were heroic measures to help him or were efforts to annihilate him. His autism was a "rejection-approach," in which the child rejected the parents' contacts with him while behaving in such a way that the parents constantly had to make heroic contacts with him.

The child would repeatedly place himself in danger in ways—such as dashing in front of moving cars—that caught the parents' eyes, and force them to react or the child would be injured or killed.

Such death-defying behavior forced the child and

parents to repeat over and over the experience similar to the death-threatening situation of the child's infancy. The child wanted the parents to rescue him without also threatening to kill him. The child's behavior, however, constantly aroused parental rejection and threatened to re-arouse the death wishes in the parents.

This history highlights some of the main struggles of the autistic child and his parents. The rationalized death wish, combined with intense love and heroic efforts, produces an intense emotional approach-rejection behavior pattern in the parents.

The parents at times become professionals in the field of autism, i.e., special education, psychology, or psychiatry. A close look at the writings and work of such parents usually reflect this approach-rejection, i.e., they show a dedicated effort to deal with the diagnosis and treatment of the autistic child, but in ways that reject the recognition of autistical issues.

The Schizophrenic Child

Clinical Observation

The schizophrenic child tends to be a scattered child. His personality is like a broken dish or a handful of sand that has been thrown into the wind.

He fragments and confuses in the most ingenious manners. For example, his words frequently make no sense to the observer. Suddenly, however, the observer discovers that there is a sort of secret message in what is being said or done.

Also, he frequently reacts to the symbols of objects or behaviors rather than to the actual objects or behaviors. He reacts to symbolic fragments of conversations rather than to the total meaning of the conversation.

Similarly, he tries to communicate to others with behavior that is symbolic or tries to communicate vast ideas with fragmented symbolic speech.

Hallucinations often are present; or he may live in a fantasy world that he takes quite seriously.

Other symptoms—similar to those of the autistic child—may include some of the following. He sustains odd play, with an inappropriate attachment to objects. He exhibits marked physical overactivity. He laughs and giggles inappropriately. He is not cuddly. He resists learning. He has difficulty mixing with other children and hides himself by identifying with scattered parts of the environment.

Paranoid delusions underlie many of these symptoms.

History

The schizophrenic child's disturbance is frequently not recognized until a more advanced age than that of the autisitic child or the mentally retarded child. The child may have what appears to be a very normal history until two to four years of age; he then starts behaving oddly.

Other schizophrenic children may appear normal until adolescence; then, the psychosis is recognized.

Early history will usually reveal that the child experienced, like many children, some marked immaturity (learning difficulties, bed wetting, speech defects, severe inhibitions, hyperactive behavior, early feeding difficulties, etc.) but that he did not outgrow it.

Excessive use of very immature fantasy play in which the unrealness is taken very seriously is often in the history.

Some schizophrenic children have histories which are similar to those of autistic children. Early in life, these children appear autistic. Later, they appear schizophrenic. Or, some psychotic children develop, initially, a schizophrenia which later becomes autism.

Family Dynamics

A mother or father of the schizophrenic child often plays a chronic game of emotional tug of war with the child—with conflicting demands and indulgences of the child.

The mother frequently gives the child contradictory messages or orders so that if the child follows one order he is, at the same time, disobeying another order. For example, the mother requests the child to be affectionate to her and when he is, she responds affectionately. The next time the child is affectionate, however, she rejects his affection.

So the child may have a clear picture of the mother's desire and love for the child and know how to obtain that love. However, to obtain this love the child must disobey another of her desires which brings a rejection or later rejection. Thus for every pleasure the child feels he has some suffering and rejection to pay. The schizophrenia becomes a self-imposed punishment and rejection.

Tragedy also tends to be in the schizophrenic child's family tree. There often have been deaths of other children in the family, death in the parents' family during their childhood, or early deaths of parents while all the children are still young.

Organic Mental Retardation

Clinical Observation

When organic mental retardation is being entertained as a possible diagnosis, physical conditions or definite evidence of severe neurological brain damage or other congenital physical anomolies associated with organic retardation must be found. Thus, physical causes such as PKU, cretinism, mongolism, hydrocephalism, give generally definitive diagnosis as the primary cause of the retardation. But conditions such as birth anoxia, forceps delivery, or hyperactivity with minimum neurological findings in themselves do not allow definite diagnosis as primarily neurologically caused retardation in a low functioning child.

A retarded child generally behaves more grossly than a psychotic child. Thus, his manipulative behavior usually is more obviously manipulative and less offensive than that of the psychotic child.

Physically, the retarded child is usually less well-proportioned than the psychotic child and frequently his physical growth is inhibited, although if psychoses develop to a severe degree growth may be inhibited.

Finally, general observations of the behavior of an organically retarded child will show that contacts—visual, verbal, and physical—with others tend to be fairly direct.

History

With most children, there is either a history of consistent low function from the onset of the causes of the retardation or a gradual progress of the retardation. The parents may discover that the child at an early age is unable to hold or manipulate objects, or has uncoordinated body movements. This picture differs from that of the psychotic child whose physical disabilities at an early age are expressed through withdrawn behavior, bizarre immaturity, confusion, or negativeness. Sudden onsets of the retardation, after an illness such as encephelitus are not necessarily indications of retardation, as such an illness also can precipitate psychosis in an immature child.

Family Dynamics

There is no particular personality type or disorder characterizing the parent of the retarded child. However, there usually is a reservoir of guilt in the parents—they feel responsible or ashamed of the child's retardation. It usually is difficult to observe these feelings as they are frequently held under rigid control. Patience, with empathy, for the retarded child are usually the more obvious behaviors seen in the parents, when around the child, although some parents may avoid the child as much as possible. Others may take care and even cling to the child as though he is their perpetual baby. Deep rage in the parent toward the child may be present, but usually is deeply suppressed.

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Venereal Disease

The Red Door

A New Venereal Disease Clinic Concept

Results after Two Years

CHARLES S. MAHAN, M.D.*

The Red Door, a venereal disease clinic staffed primarily by non-physician health providers, was established to meet the increased case-load of the current gonorrhea epidemic. After two years of operation it has proved to be an economical, efficient new vehicle for providing good health care for persons with uncomplicated venereal diseases.

THE CURRENT VENEREAL DISEASE (V.D.) epidemic caught many parts of our United States with their "clinics down." Minneapolis was typical of most cities in having grossly inadequate facilities for inexpensive, rapid treatment. This was noted by a World Health Organization team of international V.D. experts who toured the Twin City treatment centers in 1971.

The majority of Minnesotans were being treated in private physicians' offices and still are but in small numbers. It was found that many adolescents were refraining from seeking treatment because of the high cost and/or the lack of confidentiality. Teen clinics and free clinics, and the passage of the Act for Medical Treatment of Minors in 1971 all helped to bridge the gap, but many still lacked access to treatment. Meanwhile the numbers of gonorrhea cases in Minnesota climbed by the tens of thousands.

Public and professional concern and some pressure from the media[1] brought about a call by Hennepin County health overseers for rapid development of a cheap, efficient solution to the problem. Four months later the Red Door opened at 625 Park Avenue, Minneapolis. The details of its development, a unique cooperation between city, state, and county governments, are currently being prepared for publication.

The Red Door goals are listed in the Figure. The clinic is supervised epidemiologically by the Minneapolis V.D. Control Officer, administratively by a General Hospital ambulatory care administrator, and medically by the General Hospital Obstetric and Gynecology Department. The non-physician health providers do the majority of the diagnostic and therapeutic work under specific, detailed standing orders. The clinic staff has grown from eight people on opening day to 15 at present. Physicians are called to see all cases of syphilis and all complications of the other sexually-transmitted diseases. Immediate consultation is available from the hospital OB-GYN Department or emergency room staff when needed.

The Red Door
Goals and Objectives

1. **Correctly diagnose and treat syphilis, gonorrhea and other sexually-transmitted diseases.**
2. **Provide an appropriate V.D. treatment site.**
3. **Provide intensive follow-up for treated patients.**
4. **Provide education and counsel for persons with V.D.**
5. **Demonstrate importance of an accessible clinic to V.D. control.**
6. **Serve as resource and referral center for area physicians, hospitals, clinics, and schools.**
7. **To do all the above confidentially and at the lowest possible cost to the taxpayer.**

Figure

Results

During the two year period from clinic opening in February 1972 to February 1974, 23,940 people were seen at the Red Door for sexually-transmitted diseases. Most of these were new or "first-time" visits (Table 1). Seventy-six persons

*Associate Professor, Department of Obstetrics and Gynecology, Hennepin County General Hospital and University of Minnesota Medical School and Medical Director, Red Door Venereal Disease Clinic.

Present address: Department of Obstetrics and Gynecology, University of Florida College of Medicine, Gainesville, Florida 32610.

TABLE 1
Number of Visits
February 1972 to February 1974

	Number	Percent
New	15,121	63%
Follow-up	3,441	15%
Repeats	5,378	22%
Total	23,940	

made over 10 visits!

Of the total visits, 21,675 persons referred themselves or were referred by private physicians or other health providers. The others, 2,265, were referred in by their sexual contacts who had previously been to the Red Door.

Age, Sex and Marital Status of Clients

Men outnumbered women by 14,569 (61%) to 9,371 (39%). The age distribution for the two sexes was similar and is combined with the positive V.D. rate for each group in Table 2. Seventy-six percent of men seen were single as were 76% of women. Married men over 25 outnumbered married women in that age group by four to one. (Accuracy of honest answers to the question of marital status in venereal disease clinics is notoriously low.)

Geographic Distribution

The lion's share of the funding for the Red Door is provided by Hennepin County government, and so it is of interest to compare residence of clients between the three governments participating in the clinic. Table 3 includes out-of-state clients.

Cases of Gonorrhea

Of the total number of clients seen, 19% (4,483) had gonorrhea. Men had an 18% (2,636) and women a 20% (1,847) incidence of infection.

Epidemiologic treatment (treatment of a confirmed contact to an infected person before culture results are back) was administered to 416 men and 526 women.

Antibiotics used are noted in Table 4 for the total number of clients with gonorrhea. Penicillin is our drug of first choice and has had a 98.7% cure rate at the Red Door (known only for those persons returning for test of cure).

Orifices in which gonococci were found, in-

TABLE 2
Age Distribution by Sex

Men							
Age	10-14	15-19	20-24	25-29	30-34	35-39	Over 40
Total Number	21	1,683	6,279	3,646	1,435	648	857
% of Total	0	12	43	25	10	4	6
Total Number with Gonorrhea	3	290	1,133	703	290	98	119
% of Total	0	11	43	27	11	4	5
Women							
Age	10-14	15-19	20-24	25-29	30-34	35-49	Over 40
Total Number	112	2,746	4,531	1,221	371	172	218
% of Total	1	29	48	13	4	2	2
Total Number with Gonorrhea	29	590	893	222	70	23	20
% of Total	2	32	48	12	4	1	1

TABLE 3
Residency of Clients

	Minneapolis	Other Hennepin County	Other Minnesota	Out of State
Total No.	16,441	4,055	2,820	624
Percent	69	17	12	3
Clients with Positive V.D. Tests	3,551	561	377	109
Percent	77	12	8	2

TABLE 4
Antibiotic Treatment of Gonorrhea

Drug	No. Treated	%	Total Cost	Unit Cost to County
Penicillin	3,734	61.7	$5,974.40	$1.60/4.8 mill. units
Tetracycline	2,191	36.2	701.12	0.32/9 grams
Spectinomycin	86	1.4	593.40	6.90/4 grams
Erythromycin	37	0.7	119.88	3.24/15 grams

All Antibiotics = $7,388.80

cluding multiple sites in the same patients, are shown in Table 5.

Cases of Syphilis

A total of 118 cases of syphilis were seen with 90 men and 28 women making up the group.

A display of syphilis by luetic stage, sex and age group is seen in Table 6.

Fifty-four women and 137 men were epidemiologically treated for syphilis, a total of 191.

Two of the 28 women with syphilis also had gonorrhea cultured from the cervix.

Other Sexually-Transmitted Diseases

Table 7 lists other diseases found and treated in men and women clients and compares them to the number of cases of gonorrhea. Statistics are not kept for complications of gonorrhea (salpingitis, arthritis, etc.) since treatment of those are beyond the scope of clinic protocol and they are referred for hospitalization or elsewhere.

Cost of Clinic

Table 8 compares yearly expenses and income and the tabulated cost of seeing a client. This is compared to the cost of similar diagnosis and treatment for clients with venereal disease in the

TABLE 8
Cost Comparison of Red Door Operation—1973
100 Clients

61% men with 17% V.D. rate
39% women with 19% V.D. rate

Red Door Cost		H.C.G.H. ER Cost	
Men	$7.66/Client	Men	$12.43/Client
Women	$4.91/Client	Women	$ 7.91/Client
Total=$1,257/100 clients		Total=$2,034/100 clients	

Savings in 1973=$777.00/100 clients

TABLE 5
Positive Tests for Gonorrhea by Orifice

Men

Urethra Only	Rectum Only	Pharynx Only	Urethra and Rectum	Pharynx and Rectum	Pharynx and Urethra	Pharynx and Urethra and Rectum
2,500	97	20	14	3	1	1

Women

Cervix Only	Rectum Only	Cervix and Rectum	Pharynx Only	Pharynx and Cervix	Pharynx and Rectum	Pharynx and Cervix and Rectum
1,587	35	199	15	9	0	2

TABLE 6
Cases of Syphilis by Stage, Age, and Sex

	Age:	10-14	15-19	20-24	25-29	30-34	35-39	40-99	Total
Primary & Secondary Syphilis	Men	0	4	14	13	6	5	10	52
	Women	0	8	4	0	0	0	0	12
Early Latent Syphilis	Men	0	2	12	6	8	3	3	34
	Women	0	3	5	3	1	0	1	13
Late Latent Syphilis	Men	0	0	0	4	0	0	0	4
	Women	0	1	1	0	0	0	1	3

TABLE 7
Other Sexually-Transmitted Diseases Diagnosed and Treated Compared to Incidence of Gonorrhea and Syphilis

	Gonorrhea	Non-Specific Urethritis	*Condyloma Accuminata	*Trichomonas Vaginitis	Non-Specific Vaginitis	Monilia Vaginitis	*Crab Lice	*Herpes Genitalis	Syphilis
Men	2,634	1,297							90
Women	1,846		950	845	829	775	477	105	28

*Statistics not kept for males.

Hennepin County General Hospital emergency room. To make the costs comparable, 100 patients were cost-analyzed in both settings given the actual sex mixture and positive-venereal-disease-rate for the Red Door for 1973.

Discussion

The unexpected large volume of business done by the Red Door and the ability to do this at reasonably low cost seem to justify its establishment. Original projections during the planning process were 20-30 client visits per day at the most. Within months after opening, visits were up to 60-80 per day and sometimes as high as 100.

The Red Door has become the prime source of referral for private medicine for darkfield exams of suspicious lesions. Clients are then referred back to the original physician for treatment.

To protect confidentiality, the client is asked to contact the Red Door for laboratory results, and the treated client is asked to contact and refer in his or her sexual partners. Only 30% of the clients return as asked for a test of cure. This is higher than other venereal disease clinics across the U.S. Obviously, cure rate in Red Door clients can be questioned as long as so few are returning for confirmation of cure.

More men than women are seen at the Red Door probably because fewer men than women have established themselves with primary care physicians. The largest number of men seen fell in the 20-30 year age group, with 15-25 years being the peak for women. This is similar to national statistics and has been explained by noting that many young sexually active women have male partners 5-10 years older.

The clinic is used most heavily by Minneapolis residents. The suburban areas of Hennepin County with both the highest number of visits and positive gonorrhea tests were Bloomington, St. Louis Park, Richfield and Edina, in order of decreasing frequency. Of these suburbs only Bloomington offers a public V.D. screening and treatment program. A surprising number of clients came from distant counties in Minnesota and from out of state. Confidential, low-cost treatment facilities in Minnesota are almost nonexistent out of the Twin City metropolitan area. However the rate of gonorrhea is much lower in small towns and rural areas of Minnesota.[2]

The 19% overall positive gonorrhea test incidence at the Red Door compares with a 25% incidence at other V.D. clinics across the U.S.[3] Our incidence has fallen from 22% when the clinic opened, probably due to aggressive case finding by Minneapolis Health Department V.D. investigators in conjunction with the national gonorrhea screening program for women.

Epidemiologic treatment of people with a partner with proven gonorrhea or syphilis is a time-proven public health measure. This is especially important when dealing with possible gonorrhea in women since cultures are only 85-90% accurate under the best of conditions, and in the three to five days of waiting for culture results salpingitis may develop. Since the majority of women and an increasing percentage of men are asymptomatic with acute gonorrhea, epidemiologic measures of treatment and contact tracing are growing more and more important.[4] Any woman seen at the Red Door with lower abdominal pain is immediately checked by a gynecologist since early hospitalization and aggressive treatment of salpingitis is essential to prevention of future sterility.

Procaine penicillin continues to be the keystone of our antibiotic treatment of gonorrhea. Our incidence of anaphylactic reactions (as distinguished from simple faints or procaine reactions) is higher than reported for U.S. Public Health Service clinics.[5] Prompt, aggressive management by clinic health providers, who have been drilled in anaphylaxis treatment and cardiopulmonary resuscitation, has resulted in quick recovery of these people. A red emergency phone provides immediate contact with and response from the H.C.G.H. emergency room. Outlined below is the most serious case of anaphylaxis that occurred.

> On the fourth day after the Red Door opened, the 73rd patient, a 21-year-old homosexual male with a negative history of penicillin allergy, received procaine penicillin 2.4 million units I.M. one-half hour after one gram of probenecid had been given orally for a positive gonorrhea smear from the urethra. Within twenty seconds after injection he complained of dizziness. He then exhibited convulsive behavior, rolling off the chair to the floor with his knees drawn up to his chest. He was wheezing, clutching at his throat and obviously in severe respiratory distress. His head was held back and an oral airway inserted as 2 cc. of epinephrine 1:1000 solution was injected subcutaneously. His face was deep blue for 60 seconds more and then the process began to reverse rapidly. By then physician help had arrived

from the emergency room and the worst was over. He was hospitalized for observation overnight and released with written information about his penicillin allergy and an encouragement to have an identification tag made. He has been seen one time since and treated for acute gonococcal urethritis with tetracycline without incident.

Our experience has taught us that it is *essential* to have epinephrine 1:1000 solution ready in a tubex syringe so that it can be reached and injected within seconds of when the patient first notices the symptoms of anaphylaxis.

Oral ampicillin in a single dose with probenecid is being used in the clinic with greater frequency and if studies currently being done indicate it is as effective as procaine penicillin in eliminating incubating syphilis, the Red Door will switch to ampicillin as the drug of first choice.[6] Spectinomycin is used sparingly because of its expense and the high cure rate with penicillin. No advantages of doxycycline or minocycline over generic tetracycline have been found which would justify the fact that they cost 30-60 times more per tablet than generic tetracycline.

The highest frequency of positive gonorrhea tests from both rectum and pharynx in men was in homosexuals. Most of the Red Door's known treatment failures have been in homosexual men either due to resistant organisms or reinfection. All "resistant" cases have eventually been cured.

The number of positive cultures of "rectum only" in women has been significant but too small to justify routine anal screening of all women in private offices. There has been a high cure rate of rectal gonorrhea with the usual penicillin regimen. Most cases of pharyngeal gonorrhea in women were picked up by asking about sore throat or participation in fellatio.[7]

Early syphilis is present in Minnesota, however, in rather low numbers. Since premarital tests are ineffective at case-finding, screening at the time of driver's license renewal is suggested as a means of turning up positive serologies in a good cross-section of the citizenry of Minnesota.

Genital ulcers should have darkfield examinations. Three women seen at the Red Door with primary syphilis had darkfield-positive exams from tiny ulcers that were multiple and typical of herpes genitalis. (One woman had both herpes and syphilis at once.) A policy of checking a serologic test for syphilis in any case of genital warts, no matter how typical they appear for condyloma accuminata, has picked up two cases of secondary syphilis in which the condyloma lata had been treated with podophyllum.

Other sexually-transmitted disease treatment makes up a large portion of drug costs at the Red Door. Non-specific urethritis is treated one time with tetracycline and referred to Urology if not cured. Vaginitis is diagnosed by immediate microscopic exam of vaginal discharge and organism-specific treatment given.

The majority of the Red Door clients have no identifiable primary health care provider. They are encouraged to find one in the private community and go there for future V. D. problems. When the clinic was established, requests were made by letter to each Minneapolis hospital chief of staff for a list of interested urologists, obstetrician-gynecologists, internists, family practitioners or dermatologists to whom referrals could be made. No answers were received.

Costs of the Red Door clinic have been kept relatively low and a good working and cross-referral relationship with General Hospital and the private medical community has been established.

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7. Wiesner PJ: Clinical spectrum of pharyngeal gonococcal infection. New Engl J Med 288:181, 1973.

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1. The Potential for Preventing Heart Attacks. (a) Background Issues and Controversies. (b) How to Reduce Risk Factors.	Henry W. Blackburn, Jr., M.D., University of Minnesota
1. Cardiac Murmurs in Children. 2. Recognition and Treatment of Acute Rheumatic Fever and Bacterial Endocarditis Prophylaxis.	James H. Moller, M.D., University of Minnesota

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Prepared by the Roerig Division of Pfizer Pharmaceuticals, the kit of more than 80 slides and a tape cassette is designed as a weapon in a campaign launched by Vivian K. Harlin, M.D., president of the American School Health Association. Dr. Harlin points out that some of the problems of pinworm or roundworm infection may be considered serious, while some are merely troublesome and that "serious" could mean such clinical manifestations as pneumonia, perforated bowel, and bloody or mucous diarrhea. Also, some of the troublesome but less serious problems may be loss of appetite, insomnia, anal itch and irritability.

Beginning with the importance of hand-washing, and trimming the nails rather than biting them, the sound-slide presentation outlines personal hygiene, and housekeeping steps to break the cycle of reinfection. Curing an infected person begins with a simple diagnostic test in which the anal area is swabbed with a scotch tape strip, which is examined under a microscope by a medical professional to detect pinworm eggs. A pleasant, single-dose treatment can then be prescribed by a physician.

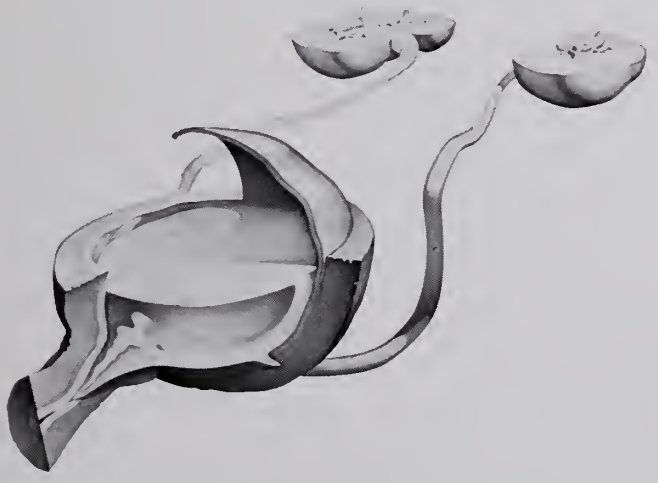
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In patients with chronic or frequently recurrent urinary tract infections

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In new multicenter studies a higher percentage of Bactrim-treated patients maintained clear cultures for four, six and eight weeks.

See charts on following page for details of studies.



For chronic cystitis or pyelonephritis evidenced by persistent bacteriuria, frequently recurrent infections or infections associated with urinary tract complications, when infection is due to susceptible organisms.

Bactrim™

(80 mg trimethoprim/400 mg sulfamethoxazole)



Before prescribing, please consult complete product information, a summary of which follows:
INDICATIONS: Chronic urinary tract infections evidenced by persistent bacteriuria (symptomatic or asymptomatic), frequently recurrent infections (relapse or reinfection), or infections associated with urinary tract complications, such as obstruction. Primarily for cystitis, pyelonephritis or pyelitis due to susceptible strains of *E. coli*, *Klebsiella-Enterobacter*, *Proteus mirabilis*, *Proteus vulgaris* and *Proteus morganii*.

Note: The increasing frequency of resistant organisms limits the usefulness of antibacterials, especially in these urinary tract infections.
The recommended quantitative disc susceptibility method (*Federal Register* 37:20527-20529, 1972) may be used to estimate bacterial susceptibility to Bactrim. A laboratory report of "Susceptible to trimethoprim-sulfamethoxazole" indicates an infection likely to respond to Bactrim therapy, "Intermediate susceptibility" also indicates a likely response and "Resistant" that response is unlikely.

Contraindications: Hypersensitivity to trimethoprim or sulfonamides; pregnancy; nursing mothers.

Warnings: Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been associated with sulfonamides. Experience with trimethoprim is much more limited but occasional interference with hematopoiesis has been reported as well as an increased incidence of thrombopenia in elderly patients on certain diuretics, primarily thiazides. Sore throat, fever, pallor, purpura or jaundice may be early signs of serious blood disorders. Frequent CBC's are recommended; therapy should be discontinued if a significantly reduced count of any formed blood element is noted. Data are insufficient to recommend use in infants and children under 12.

Precautions: Use cautiously in patients with impaired renal or hepatic function, possible folate deficiency, severe allergy or bronchial asthma. In patients with glucose-6-phosphate dehydrogenase deficiency, hemolysis, frequently dose-related, may occur. During therapy, maintain adequate fluid intake and perform frequent urinalyses, with careful microscopic examination, and renal function tests, particularly where there is impaired renal function.

Adverse Reactions: All major reactions to sulfonamides and trimethoprim are included, even if not reported with Bactrim. *Blood dyscrasias:* Agranulocytosis, aplastic anemia, megaloblastic anemia, thrombopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme, Stevens-Johnson syndrome, generalized skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Glossitis, stomatitis, nausea, emesis, abdominal pains, hepatitis, diarrhea and pancreatitis. *CNS reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo, insomnia, apathy, fatigue, muscle weakness and nervousness. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities to some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia in patients; cross-sensitivity with these agents may exist. In rats, long-term therapy with sulfonamides has produced thyroid malignancies.

DOSAGE: Not recommended for children under 12.
Usual adult dosage: 2 tablets b.i.d. for 10 to 14 days.
For patients with renal impairment:

Creatinine Clearance (ml/min)	Recommended Dosage Regimen
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15-30	2 tablets every 24 hours
Below 15	Use not recommended

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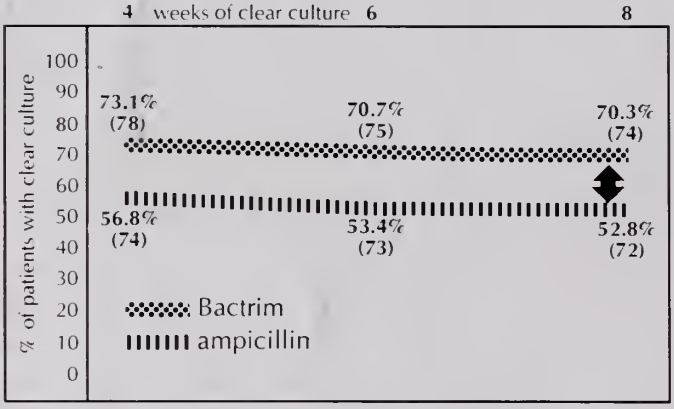
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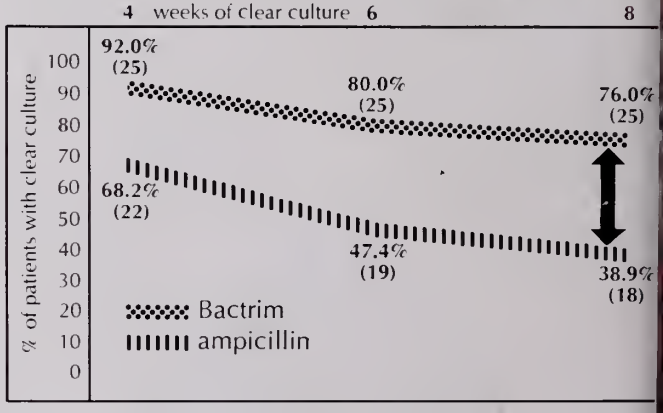
Bactrim vs ampicillin. 10-day therapy. 157 patients.



Criterion for clear culture: 1000 or fewer organisms/ml of urine.
Numbers in parentheses: No. of patients evaluated for this time period.

17.5% The Bactrim plus.
Patients maintaining clear cultures for 8 weeks
Bactrim: 70.3%
ampicillin: 52.8%

Bactrim vs ampicillin. 28-day therapy.* 53 patients.



Criterion for clear culture: 1000 or fewer organisms/ml of urine.
Numbers in parentheses: No. of patients evaluated for this time period.

37.1% The Bactrim plus.
Patients maintaining clear cultures for 8 weeks
Bactrim: 76.0%
ampicillin: 38.9%

In two multiclinic, double-blind studies of patients with chronic or frequently recurrent urinary tract infections, Bactrim maintained a higher rate of clear cultures than ampicillin. All patients had "significant bacteriuria" (100,000 or more organisms/ml of urine) on two consecutive pretreatment cultures; many had previously undergone multiple treatment programs and/or surgery. Organisms were *E. coli* and *Proteus mirabilis*.

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Please see preceding page for summary of product information.

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JULY 1975

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Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequ and/or severity of grand mal seizures require increased dosage of standard convulsant medication; abrupt withdr may be associated with temporary increase in frequency and/or severity o seizures. Advise against simultaneous gestion of alcohol and other CNS depr sants. Withdrawal symptoms (similar those with barbiturates and alcohol) h occurred following abrupt discontinu (convulsions, tremor, abdominal and cle cramps, vomiting and sweating). addiction-prone individuals under ca

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According to her major
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Valium® (diazepam)

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President's Letter



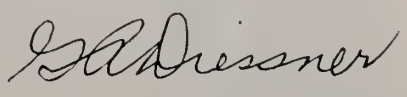
Freeloaders

Physicians no longer can afford the luxury of being freeloaders divorced from the interests and concerns of organized medicine. The medical associations' activities are supported entirely from the dues of their members. As the Minnesota State Medical Association's expanded activities have become increasingly complex and expensive, the active participation and financial support of every physician is necessary.

There was a time when potential members could feel protected from the social and economic forces around them by practicing in a medical school or group practice, or by limiting their professional activities to teaching, administration, or research. However, in recent years, governmental interest in medical education and research has grown by leaps and bounds. Only a little more than a year ago, for example, the physicians doing basic research in which fetal experimentation was a part suddenly had to look to organized medicine to assist them in legislative activities. Until this happened, they had felt little kinship with organized medicine; but there is a continuing need for organized medicine to have the input and support of all physicians who research and teach.

Others have argued that there is little reason for a physician to belong to the county medical society, Minnesota State Medical Association, or American Medical Association if he belongs to his specialty society. I look on this argument as a cover for evasion of one's legitimate obligations. There is need for both specialty and broad-based organizations to represent physicians. I welcome the increasing socioeconomic activities of the specialty societies, the Association of American Medical Colleges, and the American Group Practice Association. Each of them represents a segment of medicine with special concerns. But only the state medical societies and American Medical Association can gather the consensus and the strength of the majority. Occasionally we must accept differences in the approaches and to solutions of problems evaluated by these organizations; and I can do this. But I cannot accept these differences as a reason to "not belong" to the MSMA or the AMA.

We are now about to embark on an expanded role for the Minnesota State Medical Association by action of the House of Delegates in May. The MSMA will need increased staff to carry out the increased activities and the new activities suggested by the creation of the "entity". Our Association needs the financial support and active involvement of every physician in Minnesota. Let us identify those who are not carrying their fair share, and encourage them to become members. We all have the same stake in our profession's future, and the free ride should be over.



G. Roy Diessner, M.D.
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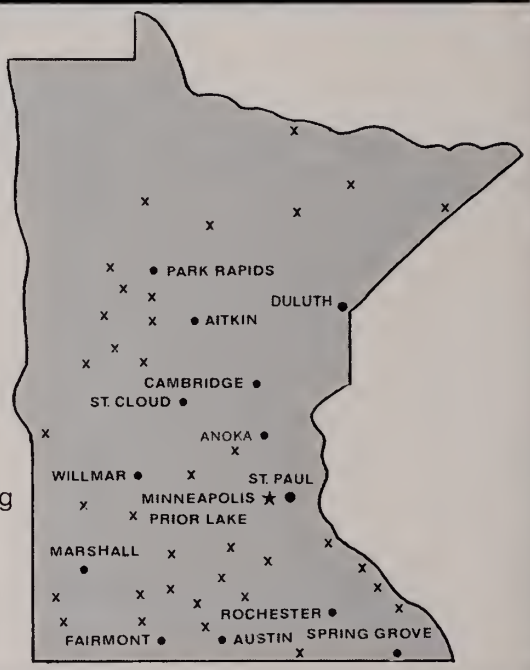
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Editor's Notebook

What Weighs Three Pounds and Wakes Up Every Morning at Six A.M.?

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The answer, if you haven't guessed already, is the Yankee Brain. The advertisement goes on to say what distinguishes the Boston bank is Yankee brains, ingenuity, integrity, and industry.

I bring up this gray matter because in late April Minneapolis had the privilege of hosting a Yankee Brain. Franz J. Ingelfinger, Editor of the NEW ENGLAND JOURNAL OF MEDICINE, was in town to speak before the Minneapolis Society of Internal Medicine. His subject was: "Medical Education: Algorithms or Algebra?"

If you're not in the know yet, an algorithm is a set of step-by-step instructions to solve a problem. Or, if you want to take a different tack, algorithms are canned, packaged, or programmed logic. Algebraic thinking, on the other hand, requires and implies general knowledge and independent problem solving.

Anyway, lately there's been a movement afoot among Health Care Providers to have non-physicians use algorithms to solve clinical problems.[1-3] The idea behind this movement is simple: if you can get enough non-physicians using enough algorithms, you can "extend" the mind of the physician to solve clinical problems without the physician really being there.

These "physician extenders", the reasoning goes, will make Medicine not only more efficient but more logical to boot. At least that's the argument Health Care Providers are advancing to push algorithms as an efficient, economical, and logical means of reducing expenses and lessening dependence on physicians.

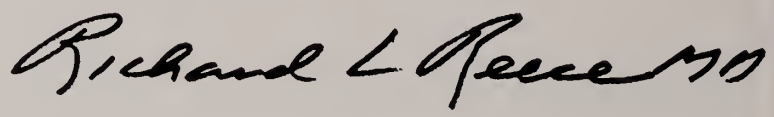
Doctor Ingelfinger isn't buying this argument. In the first place, he says algorithms are demeaning to physicians and even to their extenders. What do you have to know to use an algorithm? Well, you need to read and to speak, to follow instructions, to ask yes or no questions, to type 20 words a minute, to know a few medical terms, to carry out procedures, to be docile, and to swing from branch to branch on the decision tree. Secondly, he feels widespread algorithm use would devalue the physician as an independent thinker. After all, what would distinguish the physician from his or her extender? Thirdly, and most importantly, passive use of algorithms might discourage active use of the mind—pursuing ideas, entering into controversies, ferreting our facts, balancing merits of a case, or reading in the journals and in the libraries. In short, you can't program enquiring curiosity and a lively intellect. These traits require an independent mind and the broad education and unfettered environment that produces that kind of mind.

I agree with Doctor Ingelfinger's main point that Health Care Providers had best be wary about "extending" that three pound organ mounted in the cranial vault. Still I think algorithms have a limited place in cutting down clerical burdens, in reducing rote memory tasks, in sorting our relevant information, and in bringing

appropriate patient problems to the physician's attention. These algorithms will work best if physicians design their own algorithms for their own purposes.

Doctor Ingelfinger's talk also brings to mind two points that Peter F. Drucker has made before,[4] but are worth emphasizing again. These are the differences between: (1) efficiency and effectiveness; and (2) logic and perception. Efficiency is doing the right things and giving the right answers; effectiveness is finding the right things to do and asking the right questions. Logic is programmed or systematic thought; perception is becoming aware through your senses and intuitively putting stray bits of knowledge together.

When do these differences become important? Well, an experienced physician has the knack for perceptively sizing up a patient at a fleeting glance and asking precisely the right question. A physician extender, on the other hand, may ask all the right questions and do all the right things—and miss the patient's problem altogether.



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Pathophysiology of Trauma*

RICHARD KYLE, M.D.†

Man's response to trauma involves a complex interaction of many defense mechanisms that act to preserve vital tissue function. Man can aid these natural mechanisms only through a thorough understanding of them.

MAN RESPONDS TO trauma by mobilization of energy stores and the conservation of sodium and water. This assures glucose for the preservation of the central nervous system and the perfusion of vital organs.[13]

The mechanisms of this response are quite complex and interrelated as can be seen in Figure 1. The major activators are peripheral nerve stimulation and hypotension. Egdahl has shown in experimental animals that peripheral nerve sectioning markedly reduces the response of the pituitary adrenal axis and sympathetic systems.[7] This was confirmed in studies on trauma to limbs of paraplegics which revealed no increase in plasma ACTH or cortisol after injury.[6] Hypotension is a most potent stimulus to ACTH and ADH secretion.[12,18] Barro receptors sense reductions in blood volume and activate the pituitary adrenal axis and sympathetic system. The catecholamines from the adrenal medulla and sympathetic systems cause vasoconstriction of peripheral and visceral vessels. They also increase the rate and force of myocardial contraction.[13] Franksson and Egdahl have found that whereas cortisol production is increased in hypotension, in shock states this production is markedly reduced.[1,9,15] There is also experimental evidence that blood flow to the adrenal cortex is preferentially shunted to the adrenal medulla during shock.[15] Because of the cortisols critical role in tissue metabolism and response to stress, its exogenous administration seems mandatory in the treatment of any form of shock.

Casey found an obligatory retention of sodium and water in the immediate post traumatic period as a result of ADH and aldosterone secretion.[2] ADH conserves water to a greater extent than sodium and is elevated for at least four to five days after major surgery or trauma with hypotension.[13] Osmo receptors which normally control its secretion are not effective in the immediate post injury period. Aldosterone released by ACTH and angiotensin also acts to conserve sodium and in addition, potentiates the excretion of potassium and hydrogen.[10] Its release is immediate and a positive sodium retention may be present for as long as four days after a loss of 10-20% of plasma volume.[18] If these homostatic responses fail and hypotension persists, tissue hypoxia results in the conversion to anaerobic glycolysis. Acid-by-products buildup resulting in intravascular agglutination and increased vessel permeability. Extravasation of fluid into extravascular compartments occurs and hypotension is much greater than that accounted for by hemorrhagic loss alone.[10,16] Glomerular filtration is decreased, setting the stage for renal failure. These events may also result from hypoxia due to respiratory trauma either direct or indirect.

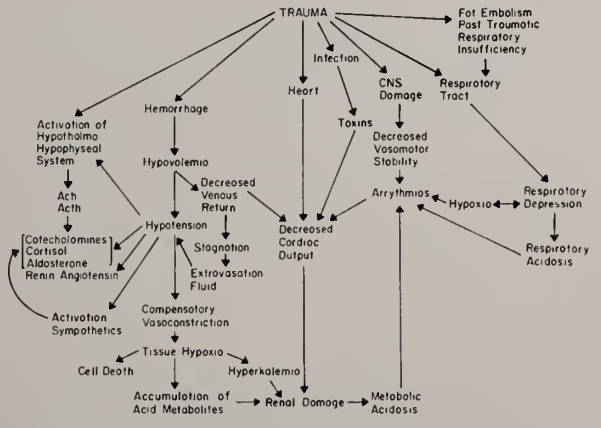


Fig. 1—Man's response to trauma is complex and involves the activation of many systems.

*Read at the Annual Orthopedic and Trauma Seminar of the Hennepin County Medical Center, Minneapolis, Minnesota November 8-9, 1974.

†Orthopedic Resident, Hennepin County Medical Center, Minneapolis, Minnesota.

Direct central nervous system trauma may lead to respiratory depression by loss of auto regulatory mechanisms. Indotoxins from infection increase capillary permeability and cause cardiac decompensation with resultant hypotension.

The metabolic response to trauma is an obligatory catabolism of protein and fat stores to provide precursors for the citric acid cycle. Moore found the degree of negative nitrogen balance was proportional to the severity of trauma.[17] McNamara also found the degree of serum free fatty acids and triglyceride elevations related to the magnitude of injury.[19] Negative nitrogen balance, as measured by urinary excretion of nitrogen, reached a maximum on the seventh post injury day in Cuthbertson's study on metabolism after fractures.[4,5] Metabolic activity was increased up to 25% from one to three weeks after multiple fractures.[4,5] Hyperglycemia and glycosuria are seen in the immediate post injury period as a result of glycogenolysis and glyconeogenesis stimulated by the catecholamines.[10] Of importance in causing elevated glucose levels is the reduction of serum insulin. This results from increased sympathetic activity inhibiting insulin secretion as well as the antagonistic action of almost all hormones elevated in the post traumatic period.[10,13]

Cuthbertson found that by increasing room temperature from 20-30 degrees and by administration of a diet high in protein and caloric content, he was able to significantly reduce nitrogen loss and decrease oxygen consumption in the catabolic period.[4,5]

At the cellular level, death may occur with the ultimate survival of the organism (Figure 2). With cell injury, histamine and serotonin are released. A short period of reactive vasoconstriction is followed by vasodilatation as a result of these enzymes and intravascular fluid is extravasated into the extravascular compartment. Leukocytes which become adherent to the endothelial lining of the venules immediately after injury preferentially migrate to the injured site. The mechanism of increased permeability is felt to be swelling of the cells, thus creating a small separation between the cell walls.[20] Proteolytic enzymes also attack the endothelial lining of vessels, increasing their permeability. Histamine and serotonin survive for only about 30 minutes.[20] The prolonged vessel permeability is mediated by the kinins. They are brought into extravascular compartments by plasma kininogens on alpha II globulins. Proteases then act upon these complexes to release kinins. Kinins act to increase vascular permeability by a mechanism similar to histamine and serotonin. This sequence of events is summarized in Figure 3. Fibrin from plasma clogs the lymphatics, leading to stasis, swelling, erythema and heat. The stasis increases hypoxia, decreasing the pH of the area. WBC's are lysed, releasing lysozymes which act to solubolize foreign bodies and necrotic tissue. Phagocytosis carried out primarily by monocytes also acts to clear the area of debris. Monocytes are not as sensitive to lysing as granulocytes and therefore, increase in number with time and are recognized as the cells of chronic inflammation.[10]

If necrotic debris and foreign bodies cannot be removed by phagocytosis and lysis, they are walled off by fibroblasts forming abscesses and granulomas. The clearing of debris from a wound by these cells marks the beginning of the repairative or fibroblastic phase. The acute inflammatory phase

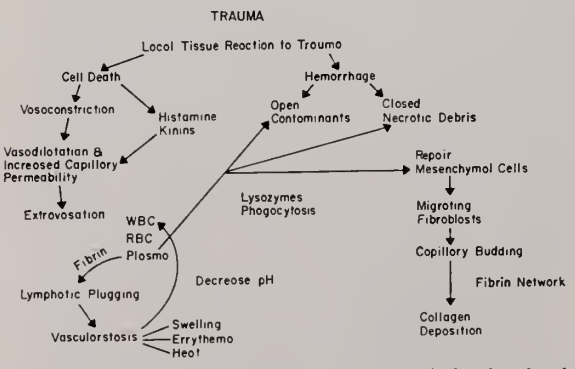


Fig. 2—Cell death usually does not result in the death of the organism and repair must be accomplished with the removal of non-viable tissue. This is done either by debridement or by the bodies natural defenses.

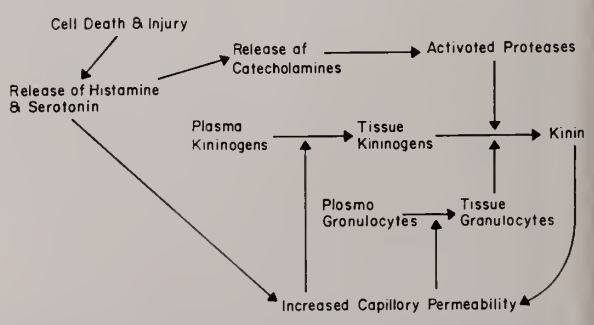


Fig. 3—Intravascular components extravasate into extravascular compartments by the action of histamine, serotonin and kinins.

lasts three to five days in clean surgical wounds.[20] The importance of hemostasis and soft tissue handling as well as thorough debridement of wounds is clearly essential for healing. Primitive mesenchymal cells close to the site of injury differentiate into migrating fibroblasts which use the wound fibrin as a framework for deposition of collagen. This period of fibroplasia is also marked by new capillary budding. Plasminogen brought in by new capillaries activates lysis of fibrin concomitant with the deposition of collagen. This repairative phase may be the best time for surgical intervention as necrotic debris has been removed and a good blood supply is present.

Of interest to Orthopedists, this timing has been confirmed by the studies of Smith, Charnley, James and Lam who all found in separate studies that the delay of at least one week in the operative fixation of long bones leads to increased callous formation and rate of union with concomitant decrease in the rate of delayed union and nonunion.[3,11,14,21] Smith and Charnley related this directly to the increased blood supply to the area after delay.[3,21]

Summary

From these studies one can conclude that immediate and adequate immobilization of injured tissue is mandatory to prevent further damage as well as further systemic response to peripheral nerve stimulation. Immediate and adequate fluid replacement is necessary to insure the perfusion of vital organs. Thorough wound debridement and gentle handling of tissue is absolutely necessary to promote the earliest possible healing. Exogenous steroid replacement is necessary in all shock states. Adequate protein and caloric intake must be provided to reduce the effects of protein and fat catabolism. Warmth throughout the immediate post injury and recovery phase should be adequate. Operative intervention of closed long bone injuries should be delayed until the area of traumatized tissue has entered the fibroblastic phase. This has occurred uniformly by the tenth post injury day in the previously mentioned studies.[3,11,14,21]

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Cover Photo

"Fourth of July"

The cover photograph was taken of the fife and drum corp during the "Fourth of July" celebration at Fort Snelling, St. Paul. If you have not seen the restored Fort, the editors urge you and your families to see it.

Analysis of 200 Multiple Trauma Patients at Hennepin County Medical Center*

JAMES TANDIAS, M.D.;† ERNEST RUIZ, M.D.‡ and RAMON GUSTILO, M.D.#

This study is a review of 200 multiple trauma patients at Hennepin County Medical Center. Their injuries were rated using a previously reported Injury Severity Scale based on the Abbreviated Injury Scale (from the AMA Committee on Medical Aspects of Automotive Safety) and correlation was again noted between severity score and patient survival.

WE HAVE SEEN IN the last few years a proliferation of measures in the evaluation, transportation and management of the trauma patient. Many statistics have been recorded as to the superiority of one mode of treatment over another, but unfortunately, these statistics are rarely truly comparable. Differences in severity are difficult to translate objectively into scalar measurements. This problem becomes compounded when the single organ or area injury is expanded to include multiple trauma, where the number of possible combinations of injuries becomes a statistician's nightmare. In many studies, coexistant trauma has been lumped together under the broad classification of "associated injuries", the effects of which undoubtedly differ. As we will see, ordinarily, nonfatal injuries in combination do seem to account for a significantly higher mortality.

The following is a review of the Stabilization Room records in the Emergency Department at Hennepin County Medical Center from September 1972 through June 1974. Using an experimental method that rates injuries by means of a standardized scale, an attempt is made to see if any conclusions can be observed.

Multiple trauma in this study, regardless of cause, is defined as the involvement of two or more of the following areas except for the extremities, where multiple long bone fractures would qualify without an additional area of involvement:

1. Head and neck
2. Chest
3. Abdomen
4. Pelvis
5. Extremities with the exception as noted above.

This group of 200 patients included 52 females and 148 males from a group of 547 trauma patients seen in the Stabilization Room. Their ages ranged from one to 88 years with the breakdown by decade as follows:

Age by Decade	Number of Patients
10 years	8
10-19	28
20-29	56
30-39	31
40-49	18
50-59	22
60-69	11
70	12

Forty-eight of these patients had a blood pressure <80 or a pulse >140 and 36 were comatose on arrival in the Emergency Room. The use of alcohol prior to injury was documented in at least 39 cases. The causes of these injuries were as follows:

	Number of Patients	
Type of Injury	By Type	Number of Deaths
Automobile accidents	50	5
Snowmobile	2	1
Pedestrians struck by vehicles	59	24
Falls	21	4
Motorcycle	11	3
Industrial crush injuries	5	1
Child abuse	2	2
Stab wounds	7	0
Gunshot wounds	38	3
Bomb	1	0
Bicycle	4	0
	200	43

*Read at the Annual Orthopedic and Trauma Seminar of the Hennepin County Medical Center, Minneapolis, Minnesota, November 8-9, 1974.

†Emergency Medicine Resident, Hennepin County Medical Center, Minneapolis, Minnesota.

‡Chief of Emergency Medicine, Hennepin County Medical Center, Minneapolis, Minnesota.

#Head, Department of Orthopedics, Hennepin County Medical Center, Minneapolis, Minnesota, and Orthopedic Surgeon, Metropolitan Medical Center.

Patterns of Involvement of Body Areas by Type of Trauma

Type of Injury	# of Patients	# of Deaths	Number of Cases Involving Each Area: Head & Neck	Chest	Abd.	Pelvis	Ext. Fx's
Automobile	50	5	16	26	27	12	26
Snowmobile	2	1	1	1	2		1
Pedestrians	59	24	42	25	31	27	44
Falls	21	4	10	12	6	8	16
Motorcycle	11	3	8	2	3	1	7
Crush	5	1	1	3	1	3	2
Child abuse	2	2	2		2		
Stabbing	7	0		7	7		
Gunshot	38	3	3	11	19	1	3*
Bomb	1	0			1		1
Bicycle	4	0	3		2	2	3

*Excludes soft tissue injuries without fracture

Patterns of Involvement in Fatal Cases

Type of Injury	# of Deaths	Head & Neck	Chest	Abd.	Pelvis	Ext. Fx's
Automobile	5	1	5	5	1	2
Snowmobile	1	1		1		1
Pedestrian	24	20	13	17	13	18
Crush	1		1		1	
Falls	4	4	4	1	2	3
Motorcycle	3	3	1	1		3
Child abuse	2	2		2		
Gunshot	3	2	1	3		

Specific Injuries by Areas

	# of Patients	# of Deaths
1. Head & Neck		
Skull & Facial Fractures	43	18
Neck Fractures	7	4
Concussion Diagnosed	51	
2. Chest		
Rib/Clavicle Fractures	51	15
Pneumothorax/Hemothorax (includes 5 flail chests)	45	17
Diaphragmatic rupture or perforation	7	1
Thoracic Vessels	4	3
Heart & Pericardium	3	2
3. Abdomen		
Spleen	29	8
Liver	32	9
Gallbladder	2	0
Bowel—including stomach	17	5
Ureter, Bladder & Urethra	13	5
Kidney (Fracture or Contusion)	15	1
Pancreas	1	0
Major Abdominal Vessel	10	3
4. Pelvis		
Pelvic Fracture	54	17
Hip (Fracture or Dislocation)	9	1
5. Extremities*		
Upper	37	
Lower	75	

*Patients may have one or more fractures. In 29 patients, open fractures were involved. There was no mortality without other injuries.

To classify trauma for comparative purposes, several approaches have been suggested:

1. One is to compare identical injuries—if such a condition exists. With Multiple trauma this is clearly not feasible.
2. The second approach is to set up a standardized rating system whereby different injuries can be classified by severity for comparison. Experience and observation can help in setting up this rating system, but it is doubtful the subjective element can be wholly eliminated.

This second approach has been used in experimental rating method based on the Abbreviated Injury Scale which was developed in 1968 by the AMA Committee on Medical Aspects of Automotive Safety. Briefly, the Abbreviated Injury Scale codes 1-5 are used to denote severity omitting the fatal codes 6-9 which are used to classify deaths within the first 24 hours. This method described in the March 1974 issue of the Journal of Trauma derives a so-called "Injury Severity Score" in which:

> $A^2 + B^2 + C^2$ = Injury severity score where A, B and C represent Abbreviated Injury Scale scores of the three most severely injured areas.

A somewhat linear relationship was demonstrated between severity of the multiple injuries and patient survival.

Case Reports

The following cases from the study are being used to demonstrate the Abbreviated Injury Scale method.

Case 1

The patient was an eight-year-old Black male admitted May 18, 1974 with an accidental gunshot wound to his right chest, while playing with a .38 caliber revolver. Physical examination on admission revealed a blood

pressure of 56/0. The wound entrance was at the right 5th rib area anteriorly. There was no visible exit wound.

Xrays revealed a bullet lodged near the T-12 body. A chest tube was placed with 250-300 cc's hemothorax evacuated. The patient was taken to the operating room where the following diagnoses were confirmed:

1. Contused right middle lobe of the lung with diaphragmatic perforation.
2. Through and through wound of the liver.

Abbreviated Injury Scale Score	
Chest	3
Abdomen	4
Injury severity score: $(3)^2 + (4)^2 = 25$	

This patient had a non-complicated hospital course and was discharged on the 10th hospital day.

Case 2

The patient was an 80-year-old male who was struck by a car while crossing a street on November 20, 1973. Physical examination revealed an initial blood pressure of 160 systolic, falling to 80-90 systolic after admission. There were numerous contusions. The chest was clear. The abdomen revealed absent bowel sounds and was diffusely tender. There was gross hematuria present. The extremities revealed a compound fracture of the distal one-third of the right tibia and fibula. Neurological exam revealed an agitated and incoherent male with no lateralizing findings.

Summary of Injuries

1. Occipital skull fracture with small right peritemporal subdural hematoma.
2. Ruptured spleen with laceration of the right lobe of the liver and a lacerated small bowel.
3. Compound fracture of the right tibia and fibula.

Abbreviated Injury Scale Score	
Head & Neck	4
Abdomen	5
Extremities	1
Injury Severity Score $(4)^2 + (5)^2 + (3)^2 = 50$	

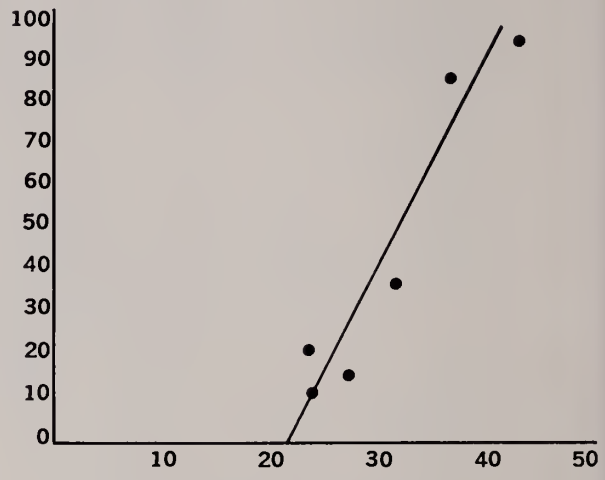
This patient had a hospital course complicated by acute renal failure and sepsis and expired on the 15th hospital day.

The following charts represent an attempt to treat our data in the same manner.

Distribution of Severity by Abbreviated Injury Scale Score

		# of Patients having each A.I.S. Score				
Area	Score	1	2	3	4	5
Head/Neck		1	20	25	15	29
Chest		1	18	55	15	7
Abdomen			3	35	53	19
Pelvis/Extremities		1	41	57	17	11

Injury Severity Score	# of Patients	# of Deaths
<25	83	1
25-50	109	34
>50	8	8



Injury Severity Score

Comparable figures from the quoted study are:

Injury Severity Score	% Mortality
35	43
43	86
50	92

Tabulating the scores for each type of injury, we find the following:

Range of Injury Severity Scores

Type of Injury	All Cases	Cases Resulting in Death
Automobile	8-50	34-50
Snowmobile	25-54	54 (1 death)
Pedestrian	8-67	22-68
Crush	1 death-score 34	
Fall	5-75	43-75
Motorcycle	17-59	34-59
Child abuse	2 deaths	36-41
Gunshot	4-50	41-50

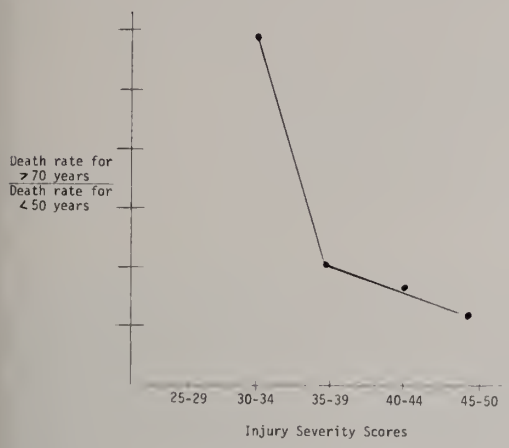
As previously noted, there were only 12 patients in the age group 70 years or older. Of the 24 pedestrian fatalities, 10 occurred in this age group, making this the single most common cause of death for this age category.

Looking at the range of fatality injury severity scores by age group, the effect of age seems to surface with increasing age:

Range of Fatal Injury Severity Scores By Age Group

Age by Decade	# of Patients	# of Deaths	Range of Fatal Scores
<10	18	4	36-41
10-19	28	5	34-57
20-29	56	4	41-59
30-39	31	5	41-75
40-49	18	3	34-59
50-59	22	6	39-50
60-69	11	2	50-59
⩾70	12	10	22-68
Age Unknown (all adults)	4	4	45-50

The effect of age can be best seen by plotting the ratio of death rates for patients 70 years of age or older and those less than 50 years old.



It can be seen that the effect of age is greatest at low scores and not unexpectedly diminishes and disappears as the Injury Severity Score approaches 50.

Discussion

In our series, several observations were made:

1. In 37 cases of head trauma with documented skull fracture, 16 patients were comatose on arrival, another 16 showed some impairment of their level of consciousness, while only five had no impairment as noted by the initial examiner.
2. Especially in the comatose multiply-injured patient, the importance of adequate cervical spine films cannot be over-emphasized. Of the seven patients in this series, there were three unrecognized cervical injuries in the Emergency Department. One C_1 fracture was not noted until the patient was in the operating room for exploratory laparotomy the second hospital day.
3. The spleen has often been mentioned as the most frequently injured organ in abdominal trauma, but in this series, liver injuries exceeded splenic injuries. Urinary tract injuries were almost as common as splenic injuries. Peritoneal lavage confirmed or excluded correctly the suspicion of intraperitoneal bleeding in 77% of the 35 taps performed with 9% false negatives and 14% false positives. One false negative tap in this series on repeat was confirmed at laparotomy.
4. Pelvis fractures occurred in over 25% of the cases. Eight of the 54 pelvic fractures were associated with bladder rupture or perforation. Seventeen other fractures were associated with some sort of urinary tract injury. The simple expediency of inserting a Foley catheter in 27 of the 28 cases of genitourinary tract injury (the lone exception being a urethral disruption preventing passage) detected gross hematuria in 25 cases, leading to further studies confirming injury. In the 26 cases cystograms and/or IVP's ensured there were three false negative studies.

It has often been assumed that the care of trauma patients has improved with advances in techniques and technology, but more measurements need to be made to help us evaluate medical care of the multiply-injured patient. To begin with, better record-keeping is necessary and the format of a problem oriented record has a very real place in the evaluation and management of the trauma patient. In the hectic atmosphere of a busy Emergency Room, it encourages the systematic documentation of data, therapeutic plan and followup for each problem, information without which subsequent review is difficult if not impossible. As we have seen, there are definite limitations of the inexact science of rating severity. This can only be improved by further observation and experience with a standardized system.

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Treatment of Acetabular Fractures*

DEAN RAU, M.D.† and RAMON B. GUSTILO, M.D.‡

An analysis is made of 70 acetabular fractures treated at Hennepin County Medical Center during the years 1970 thru 1974. A brief review of the literature pertaining to acetabular fractures and a classification of fracture types are included. Case histories, results and specific therapeutic recommendations are also presented.

DESPITE THEIR relatively frequent occurrence, the management of acetabular fractures remains a difficult and challenging problem for every orthopedic surgeon. The Orthopaedic Trauma Service at Hennepin County Medical Center during the four and one half years from January 1970 to July of 1974 cared for 70 patients with fractures of the acetabulum. These 70 cases represented 22% of 312 pelvic fractures seen during the same time. Linear non-displaced fractures, posterior lip fractures, as well as 25 central type fracture dislocations are included in this group.

Vehicle and car-pedestrian accidents were the cause of 75% of the fractures reported. Falls from heights accounted for the rest. The violent nature of these etiologic factors contributed to the multiplicity of associated injuries frequently seen in these patients.

Review of the Literature

Rowe and Lowell[13] reported on 93 fractures of the acetabulum treated initially at the Massachusetts General Hospital. They reported an overall rate of 80% good or excellent clinical results. In their series, most fractures were treated with closed methods consisting of bed rest for non-displaced fractures or skeletal traction for an average of one to two months when displacement or the femoral head subluxation were present. Following initial therapy, patients used crutches for an average of three months. In some cases, protected weight bearing was extended for five or six months. Rowe and Lowell reserved open reduction and internal fixation for unstable posterior lip fractures and bursting fractures of the superior acetabular dome. In this latter group, representing the most severe central type fracture dislocations, the rate of good results fell to 58%.

Stewart and Milford[14] stressed the need for emergency reduction of the posterior fracture dislocation of the hip. Judet[7] strongly recommended a surgical approach to all displaced acetabular fractures. They reported 173 patients, 129 of whom were treated surgically. They emphasized the need for a careful roentgenographic evaluation including internally and externally rotated oblique views. Judet expressed dissatisfaction with closed methods and stressed that the principle of anatomic reduction should be adhered to in acetabular fractures. He did not, however, report follow-up of late results of his cases. More recently, Sinning and Larson[18] described their experience with 100 fracture dislocations of the hip. The majority of their patients were treated by bed rest or traction. They emphasized, however, that if instability persists after a trial of closed methods open reduction and internal fixation are indicated. This applied especially to unstable posterior fracture dislocations and to central fracture dislocations when the acetabulum is disrupted to such an extent that it no longer held the femoral head in anatomic relationship to at least two thirds of the weight bearing dome. Harris[6] described cup arthroplasty as a salvage procedure in patients with disabling post traumatic degenerative joint disease following acetabular fractures. Rowe and Lowell also used cup arthroplasty as a means of salvaging poor late results. Their series included two cases in which cup arthroplasty was used as primary intervention in severe acetabular fractures. More recently, Coventry[2] described five cases in which total hip arthroplasty was used to treat problematic central fracture dislocations of the hip. In one of these cases, total hip arthroplasty was used as primary intervention.

*Read at the Annual Orthopedic and Trauma Seminar of the Hennepin County Medical Center, Minneapolis, Minnesota, November 8-9, 1974.

†General Surgery Resident, Hennepin County Medical Center, Minneapolis, Minnesota.

‡Head, Department of Orthopedics, Hennepin County Medical Center, Minneapolis, Minnesota and Orthopedic Surgeon, Metropolitan Medical Center.

Acetabular Fractures at Hennepin County Medical Center

Embryonically, the acetabular fossae is a deriative of the three bones of the hemi-pelvis: the ischium, ilium and the pubic bone as the coalesce in the triradiate cartilage. To maintain consistency in describing our series of acetabular fractures at Hennepin County Medical Center, we have adopted the classification of Rowe and Lowell.[13] This classification is based on the anatomical divisions of the acetabulum, but also relates to prognosis. Clinical results were evaluated by the standard used by Rowe and Lowell.[13] Followup was available in 30% of Type I fractures and 50% in Types II, III and IV fractures. Average length of followup was nine months for all patients, approximately six months for Type I fractures and 11 months for Types II, III and IV fractures. Results are tabulated in the Table.

A type I fracture is a linear non-displaced fracture of any portion of the acetabular fossa (Figure 1). There were 23 type I fractures comprising 34% of our series. Treatment consisted of bed rest followed by crutch walking until the patients could



Fig. 1—Type I—a linear non-displaced fracture.

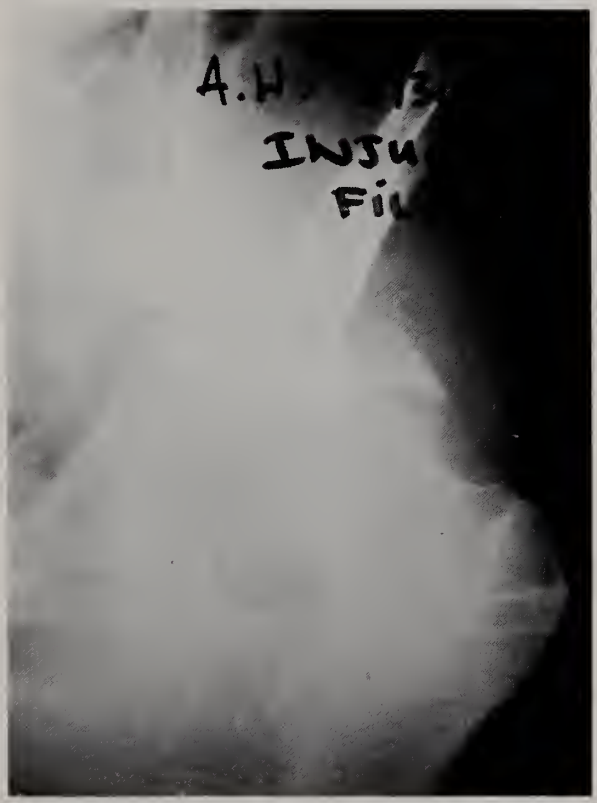


Fig. 2(a)—Type II Fracture with posterior dislocation.

TABLE

Fracture Type	Patients and Followup‡	Results Excellent	Good	Fair	Poor
I	23 Patients—7 Followup	4	3	—	—
II	12 Patients—11 With Posterior Dislocation Followup in 7	—	3	3	1
III	21 Patients—10 Followup	2	3	3	2
	14 Type III Fractures With Central Dislocation Followup in 7	1*	3†	2	1
IV	14 Patients—7 Followup	4	2	—	1
	11 Type IV Fractures With Central Dislocation Followup in 5	2	2*	—	1

*Open Reduction—Internal Fixation
†One patient salvaged with THA
‡Six Months or Longer

bear full weight without pain, usually four to eight weeks post injury. Almost uniformally, good or excellent results accompanied this fracture.

A type II fracture involves the posterior lip or the ischial portion of the acetabulum. There were 12 type II fractures which represented 16% of our series (Figure 2a). Eleven type II fractures were accompanied by a posterior dislocation of the femoral head. After emergency reduction, the hip is evaluated for stability in 30-40 degrees of flexion. If instability is present reduction is maintained with traction until the posterior lip fragments can be internally fixed (Figure 2b). Such operative approach was used in four of these 11 posterior fracture dislocations. Fifty percent of both operative and non-operative type II fractures where followup was available, had good or excellent results.



Fig. 2(b)—The same PT as Figure 2(a) after open reduction and internal fixation.



Fig. 3(b)—Same PT as Figure 3(a) reduced with 25 lbs. dismal femoral traction.

A type III fracture involves the medial innerwall which is the pubic bones contribution to the acetabular fossa. There were 21 type III fractures constituting 30% of our series. The medial inner wall of the acetabulum is relatively thin. Therefore, type III fractures are frequently accompanied by marked intrapelvic protrusion of the femoral head (Figure 3a). The 14 injuries of this type represented 58% of the 25 central fracture



Fig. 3(a)—Type III fracture with dislocation in a 19-year old involved in a motorcycle accident.



Fig. 3(c)—Same patient as Figure 3(a) one year later. A good clinical result.

dislocations in our series. Since the medial inner wall is not a major weight bearing surface, the prognosis for this type of central fracture dislocation is better than one might expect. Reduction is often easily obtained with skeletal traction applied to the distal femur or the proximal tibia (Figures 3b, 3c). Occasionally lateral traction applied to the greater trochanter is necessary (Figures 4a, 4b). Traction is maintained for an average of ten weeks. Protected weight bearing follows for an additional three to six months. If during this time the femoral head remains well reduced beneath the weight bearing dome, usually a good result occurs. The medial acetabular wall has the potential to mold itself to the femoral head during the repairative process. This phenomenon, in the presence of an intact superior dome, leads to a stable hip. If tractions fail to maintain reduction, usually a poor result ensues (Figures 5a, 5b, 5c, 5d). For this reason, persistent subluxation of the femoral head due to inadequate reduction of the medial acetabular wall is one indication for open reduction and internal fixation (Figures 6a, 6b, 6c).

In type IV fractures, the superior weight bearing dome is disrupted. Of the four types of acetabular fractures these are the most difficult to manage and in large series[13] tend to carry the poorest prognosis. There were 14 type IV fractures or 20% of our series. Usually, severe trauma and great force are required to create these fractures. Type IV fractures accompanied by inward protrusion of the femoral head represent the second type of central fracture dislocation of the hip (Figure 7a). There were 11 such fracture dislocations in the present series. If two-thirds or more of the weight bearing dome can be reduced in anatomic relationship to the femoral head, the prognosis for a type IV fracture is usual-



Fig, 4(a)—Twenty-one-year old Type II Fracture-dislocation after a fall from a four-story height.



Fig. 4(b)—Reduced with lateral traction in addition to distal femoral.



Fig. 5(a)—Seventy-three-year old struck by car. Type III fracture with central dislocation.

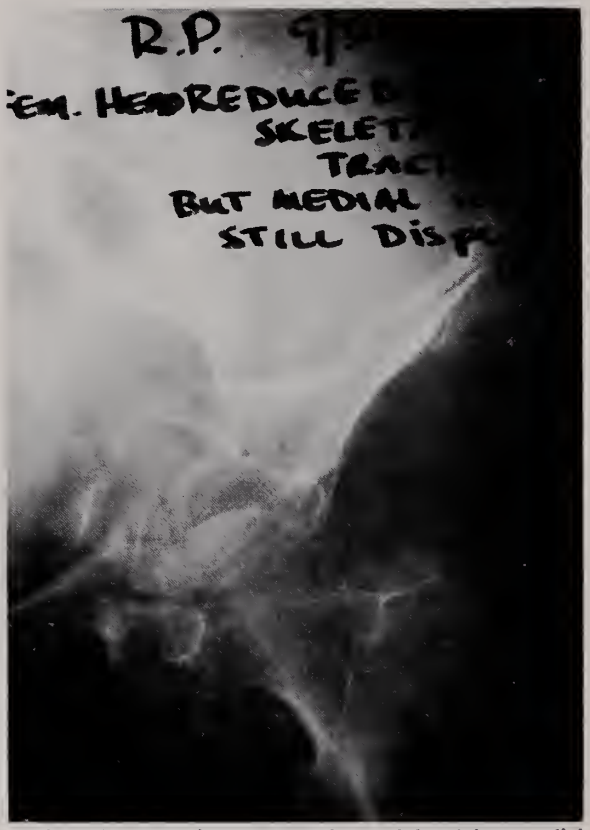


Fig. 5(b)—Traction reduces femoral head but medial inner wall is still displaced.



Fig. 5(d)—Salvaged with a total hip arthroplasty.



Fig. 5(c)—One year later the femoral head has subluxed medially. A poor clinical result.



Fig. 6(a)—Twenty-eight-year old struck by a car. Severe Type III central fracture location.



Fig. 6(b)—Femoral head reduced but medial inner wall is too displaced to maintain stable reduction.



Fig. 6(c)—Open reduction and internal fixation carried out. Eight months later has an excellent result.



Fig. 7(b)—Adequate reduction by skeletal traction.



Fig. 7(a)—Twenty-five-year old involved in an auto accident suffered a severely comminuted Type IV superior dome fracture dislocation.

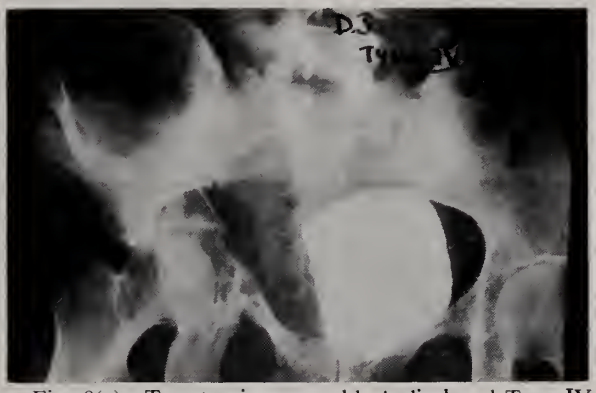


Fig. 8(a)—Twenty-nine-year old. A displaced Type IV central fracture location.



Fig. 8(b)—Fracture reduced but unstable.

ly good (Figure 7b). Traction may be successful in obtaining such reduction and is maintained for eight to ten weeks followed by four to six months of protected weight bearing on crutches. Persistent displaced fragments in type IV fractures usually lead to post-traumatic degenerative joint disease. Therefore, the inability of traction to obtain reduction is an indication for open reduction and internal fixation (Figures 8a, 8b, 8c). Careful roentgenographic evaluation including internally and externally rotated oblique views (after Judet[7]) is necessary in planning the operation. Posterior approach is most often used. Comminution makes the procedure extremely difficult. Results in this patient group showed 80% overall good results. Three patients with excellent results had minimally displaced type IV fractures. Two patients treated with open reduction had good results. There were four deaths among the 25 patients with central fracture dislocations. These were due to a variety of causes including traumatic rupture of the thoracic aorta, severe intra-abdominal trauma, shock lung, and multiple complications after a prolonged hospital course. These deaths give evidence to frequently severe nature of the trauma and complicated clinical picture associated with a central fracture dislocation of the hip.



Fig. 8(c)—One year post-open reduction and internal fixation. A good clinical result.

Recommendations and Therapeutic Guidelines

1. Make the correct anatomical diagnosis. Obtain AP and oblique roentgenogram (See 5 below).
2. Carry out emergency reduction of posterior fracture dislocations and prompt reduction of central fracture dislocations.
3. Maintain skeletal traction for 10-12 weeks when displaced central fragments or central dislocation of the femoral head have been present.
4. Continue protected weight bearing for 3-6 months depending on the severity of the fracture and the patient's symptoms.
5. Prior to open reduction of acetabular fractures, careful x-ray evaluation is essential in order to implement the correct surgical approach. Forty-five degrees anterior and posterior oblique views (Judet[7]) are imperative to localize correctly the major fragments involved.
6. Carry out open reduction and internal fixation: for unstable type II posterior fracture dislocations or when intra-articular fragments are present despite stable reduction; in type III inner wall fractures when despite traction the femoral head subluxes medially or medial wall fragments remain significantly displaced; in type IV superior dome fragments when despite traction less than two-thirds of the superior dome is in anatomic relationship to the femoral head.
7. Proceed with total hip arthroplasty for poor late results.

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9-18. Will be found on page 539.

Management of Tibial Fractures*

TERENCE KENNEDY, M.D.†, ROBERT F. PREMER, M.D.‡, SHELLY LAGAARD, M.D.# and RAMON B. GUSTILO, M.D.§

One-hundred-nine patients with 118 open and closed tibial fractures were reviewed. Closed methods with early weight bearing gave union in 98%. Pins in plaster was associated with a 62.5% delayed union rate. Using prophylactic antibiotics, all type I or II open wounds were promptly closed and there were no infections. Phemester bone grafting technique gave union in all but one patient after the initial attempt.

TIBIAL FRACTURES have always been a controversial subject as to best methods of management. There are two basic methods in use today. Primary open reduction and internal fixation is recommended by the ASIF Association for the study of internal fixation in Switzerland. Their goal is to eliminate so called "fracture disease" from prolonged immobilization in plaster, and avoid shortening and malalignment. At the opposite end of the spectrum, impressive series have been shown in the United States, supporting closed reduction in specially designed early weight bearing casts.

Our policy at Hennepin County Medical Center has always been towards closed reduction and casting methods in treating tibial fractures. Critical analysis of seventy-five closed and forty-three open tibial shaft fractures the majority of which were treated by initial long leg cast for four to six weeks followed by patellar tendon weight bearing cast until fracture healing revealed satisfactory results in over 90% of the patients. The advantages, pitfalls and complications are presented.

The General Hospital Series

Between the years 1964 and 1973 over 400 tibial shaft fractures were seen at General. This series includes 109 patients followed to union in the General Hospital Outpatient Department. All patients were eighteen years or over. Seventy-three were male, thirty-six female with an average age of forty-three years. Average hospital stay was 35.4 days (median 13) for open fractures and 12.5 days (median 8.5) for closed. Motor vehicle accidents constituted the most common mechanism of injury. There were 118 total fractures, 43 open (36%) and 75 closed (64%.) Fractures were classified as to level, type, initial displacement and comminution.

TABLE 1

Fracture Classification	No.	Percent
Type: Transverse (15 with butterfly frag.)	45	42.5
Oblique	33	31.2
Spiral	25	23.6
Segmental	3	2.8
Level: Proximal 1/3	15	14.2
Middle 1/3	40	37.7
Distal 1/3	51	48.1
Displacement:		
Minimal (less than 50%)	47	44.3
Moderate (more than 50%)	38	35.8
Non-displaced	14	13.2
Marked (no contact)	7	6.6
Comminution:		
None	22	20.8
Minimal	33	31.1
Moderate (more than 3 parts butterfly)	43	40.6
Marked (segmental or many parts)	8	7.5

Associated trauma in tibial fractures is common. The distribution in this series is as follows.

TABLE 2
Associated Injuries

Region Affected	No.	Percent
Ipsilateral femur	15	12.8
Contralateral femur	6	5.1
Contralateral tibia	9	7.7
Patella	0	
Pelvis	7	6.0
Upper extremity	7	6.0
Significant head, chest or abdominal trauma	15	12.8

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†Orthopedic Resident, Hennepin County Medical Center, Minneapolis.

‡Head, Department of Orthopaedic Surgery, Veterans Administration Hospital, Minneapolis.

#Attending Staff, Hennepin County Medical Center, Minneapolis.

§Head, Department of Orthopedics, Hennepin County Medical Center, Minneapolis, Minnesota and Orthopedic Surgeon, Metropolitan Medical Center.

Soft tissue injuries in open fractures are classified as follows:

TABLE 3
Soft Tissue Injuries

		No.	Percent
Type I	Clean puncture type wound	23	52.3
Type II	Significant size, but clean and without large areas of non-viable tissue	14	33.3
Type III	Moderate to massive wound with gross contamination and devitalized tissue	6	14.2

Treatment

Basic treatment at Hennepin County Medical Center during this period fell into eight major categories.

TABLE 4

Method		
CR-LLC	11	9.5
CR-LLC-PTB	54	54.2
CR-LLC-LLCWB	15	12.8
CR-LLC-SLWB	4	3.6
Pins in Plaster	16	13.6
Traction	0	
Primary Amputation	0	
ORIF	7	6.0

Key: CR = closed reduction
LLC = long leg cast
PTB = patellar tendon bearing cast
LLC-WB = long leg weight bearing cast
SLW = short leg walker
ORIF = open reduction & internal fixation

Average time of placement into a PTB cast is seven weeks, long leg weight bearing cast 11.9 weeks, and Delbe splint 16.4 weeks with a duration of 4.1 weeks being average.

The management of soft tissue wound in open fracture is summarized in the following table.

TABLE 5

Management	No.	Percent
Primary closure with debridement and antibiotic coverage	34	79
Secondary closure	6	14
Primary split grafting	3	7
Multiple debridement and grafting over a long period	5	11.6

Results of Treatment

Considered together, all fractures healed in an average time of 25.1 weeks. An open fracture takes considerably longer to heal—34.2 weeks (median 28 weeks) than a closed fracture—average 21.1 weeks (median 19.5 weeks.) Because of difficulty in followup, the definition of union in our series is the time the patient is let out of plaster, providing that union is confirmed on Xray.

Of the 106 fractures followed to union, there were Xrays available on only 82. The remainder of the films were unobtainable or had been destroyed. Chart notations and Radiologist's reports were used to determine fracture type, location, and displacement in these patients.

The results of treatment and healing time were correlated with several variables.

TABLE 6
Method of Treatment

Method	Weeks to Union No.	Weeks to Union Avg.	Mean	Delayed Union	Percent
LLC-PTB	54	19.4	20.5	1	1.9
LLC-LLCWB	15	23.4	21.5	0	
LLC-SLW	4	28.7	22.5	0	
Pins in Plaster	16	45.5	43.0	10	62.5
ORIF	6	37.7	33.0	1	6.3
LLC alone	11	26.6	18.5	2	18.1

It can be seen from this Table that of seventy-three fractures treated with closed methods, there was only one delayed union. All of these patients were allowed to bear weight in plaster, usually after six to seven weeks.

Rate of union versus displacement and comminution were also analyzed. Most fractures with minimal initial displacement and comminution were oblique or spiral. These are commonly low energy fractures and the incidence of delayed union is low.

Most of the fractures with marked displacement and comminution were found to be transverse or butterfly types, branding these as a high energy type. The incidence of delayed union in this group is characteristically higher.

The level of the fracture is sometimes felt to be significant in healing. In our series, over 50% of the delayed unions were in the middle third of the shaft.

Complications

Delayed Union

Delayed union in this study involved the time the clinical diagnosis was made on each patient, and not by pure radiographic findings. Pain, clinical motion of the fracture site, and X-ray findings all go hand in hand in arriving at this diagnosis. Delayed union occurred in a total of 14 patients for an incidence of 13.2%. There were eleven open fractures (25.6%) and three closed (4% total.) In reviewing the treatment methods used, ten patients had initial treatment with pins in plaster (71.4%), five of these had an ipsilateral femur fracture. One patient had open reduction and internal fixation with two screws, and two had closed reduction with remanipulation after

10-14 days. Sixteen total patients were treated with pins in plaster with delayed union in ten, a 62.5% incidence. The group that healed was compared with the group going on to delayed union regarding certain variables that could possibly contribute to this problem.

TABLE 7
Pins in Plaster Treatment

	Healed (6)	Delayed Union (10)
Average Age	26	35
Open Fracture	40%	91%
Time to Pins Out (weeks)	9.2	8
Use of PTB after Pins Out	40%	54%
Ipsilateral Femur	80%	36.4%

Treatment of delayed union in all but one case was a Phemister type cancellous bone graft usually via a posterolateral approach. Average time of grafting was 30.0 weeks (mean 26.5.) Average time to union after grafting was 22.4 weeks (mean 18.5). Average total time to union was 54.9 weeks (mean 52). All patients except for one healed after the initial graft. One patient had a fibular osteotomy at twenty-three weeks with union 13.5 weeks later.

Infection

In reviewing infections in open fractures, all type I and II wounds primarily closed with appropriate debridement and antibiotics, healed without infection. The total number of infections was four (3.8%). All of these occurred in type III wounds; one of which was initially closed, and the other two left open. One of these required an amputation at a later date and died from sepsis. The last patient had a primary Lottes nail that became infected. Of the three patients living, all had coagulase positive staph as the infecting organism. Two cleared with debridement and antibiotic therapy. The infected nail was removed, but the patient has continued to drain for several years.

Other Complications

Fat emboli complicated four fractures (3.8%), comprising the third most common complication. Of these, two had an ipsilateral femur fracture. The other two (2.7%) had isolated tibias. All recovered with supportive treatment.

There were three documented nerve palsys. All involved the common peroneal nerve. One was present on admission and later resolved. One occurred in a patient casted in the Emergency Room and sent out. This may have been a compartment syndrome and cleared when the cast was changed. One developed during outpatient followup and was of unknown etiology. It was unresolved at the time of final followup.

Deformity

The lack of adequate clinical notation made evaluation of deformity difficult, particularly shortening. All evaluation of deformity was done by Xray (82 fractures) with the findings summarized below.

TABLE 8

	Greater than 5	Greater than 10	Total
Anterior or posterior Angulation	8	3	11
Varus	1		1
Valgus	3	1	4
Present in two Planes		6	6

The total incidence of angulation greater than 5 degrees was 11.3% and greater than 10 degrees was 9.4%. 1.3% had angulation less than 5 degrees and 9.4% had angulation less than 10 degrees.

Deaths

Death occurred in twelve patients. Nine deaths were related to multiple trauma, two from myocardial infarction in elderly patients, and one related to sepsis from an open fracture.

Discussion

The overall results of this series seem to indicate that in the absence of severe soft tissue trauma or associated injuries, predictably good results can be obtained using closed methods. This is borne out in the sixty-nine patients treated by closed reduction and long leg cast with a later PTB or long leg walker, with only one delayed union, and a mean healing time around twenty weeks.

This correlates with Sarmiento's[1] series in which over one hundred open and closed fractures were treated without a delayed union using the specially designed PTB cast. Denhe[2,3] from the U.S. Army has also reported 207 fractures followed to primary union using long leg weight bearing casts. All of these authors feel that ½ to ¾ inch of shortening is acceptable in light of the high incidence of primary union.

It also appears evident that open fractures with type I or II wounds can be safely closed primarily, providing adequate debridement is carried out and high doses of pre and postoperative antibiotics are used. There were thirty-seven of these types primarily closed without complication.

A very striking fact to come out of this study was the alarmingly high incidence of delayed union using the pins in plaster technique.

Delayed union was observed in ten out of sixteen treated by this method. The presence of an ipsilateral femur, time of pin removal, or after treatment in a PTB cast did not correlate with the development of delayed union. The incidence of open fracture, however, was higher (91%) in those going on to delayed union, than those healed (40%). Good results have been obtained, however, by other authors using pins in plaster. Anderson[6] reported 107 patients so treated with only a 5% rate of delayed union. Pin removal was five to six weeks with a walking cast afterwards.

The Phemister type cancellous bone grafting technique demonstrated excellent results, and for this reason, early grafting might be indicated to those patients who by necessity required pins in plaster treatment, and are not showing good signs of healing around 12-14 weeks. This applies to other fractures as well.

A small number of patients underwent internal fixation. There were no plates used primarily, only screws in six, and a primary Lottes nail in one open fracture. No definite advantage was gained from the screws, and the patient with the Lottes nail developed chronic osteomyelitis, and has drained for years.

Although this small number of internally fixed fractures is not significant in our series, Smith[5] has recently reported a 33% serious complication rate in 219 fractures internally fixed primarily and 13% serious problems in seventy-eight fractures opened 1-3 weeks post injury.

It appears then that closed methods can give highly acceptable results. Pins in plaster is used only where absolutely necessary, and then with great care.

We virtually never open a closed tibia and rarely internally fix open fractures. In the presence of severe soft tissue or vascular damage rigid external compression devices with pins seem safer than plates or intermedullary fixation in these fractures.

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Seminars in Rheumatology

Sponsored by the Committee on Rheumatic Diseases, Minnesota State Medical Association and made possible through a grant from Syntex Laboratories, Inc. Presented at Breezy Point Resort, Breezy Point, Minnesota, July 9-11, 1975.

Topics to be covered by lecture and question and answer periods: diagnosis, differential diagnosis, pathophysiology and treatment of some of the rheumatic diseases, as well as some common symptom complexes. Systemic lupus erythematosus, rheumatoid arthritis, progressive systemic sclerosis, polymyositis, mixed connective tissue disease, Sjogren's syndrome gout, infectious arthritis, Reiter's syndrome and polymyalgia rheumatica will be reviewed. The value of synovial fluid analysis and the HLA-W27 antigen will be presented.

For more information regarding seminar registration and accommodations, call or write the Minnesota State Medical Association, CME Department, 375 Jackson, St. Paul 55101.

Acute Renal Failure in the Post-Traumatic Patient*

DONALD GRAHAM, M.D.† and ROBERT ANDERSEN, M.D.†

This paper presents five severely injured acute renal failure patients seen at Hennepin County Medical Center over a one year period and will discuss the prevention, diagnosis and treatment of this serious problem.

ACUTE RENAL FAILURE (ARF) is an acute impairment of renal function not reversible by manipulative extrarenal factors which leads to the accumulation of metabolic and other waste products. It occurs in many clinical situations and presents problems in prevention, diagnosis and management.

Most patients will require dialysis in management and will require transfer to a dialysis center. Hennepin County Medical Center (HCMC) is a center of acute and chronic renal failure patients from a five state area. Patients referred are managed by the combined Nephrology and Surgical Services.

This paper presents five trauma related patients seen or referred to HCMC during the period from July 1973 to August 1974. These patients represent different aspects of ARF, and represent about five percent of acute renal failure patients.

Mortality

Despite hemodialysis, the mortality from acute renal failure has remained high. Studies from World War II, Korea, Vietnam, and Saint Paul Ramsey Hospital have shown a 90%, 68%, 63%, and 65% mortality respectively.[1,19] University of Minnesota data showed a postsurgical traumatic mortality of 69%, post-transplant acute tubular necrosis of 5%, and the mortality of acute tubular necrosis from primary renal diseases of 41%. The incidence of ARF has decreased from 10% and 43% seriously injured patients in World War II, 0.5% in Korea, 0.2% in Vietnam, and 2.8% at Saint Paul Ramsey Hospital.[1,19] Differences in the incidence between Korea and Vietnam were attributed to an evacuation time of 35-40 minutes in Vietnam vs. three and a half hours in Korea, immediate availability of appropriate volume replacement therapy, definitive medical and surgical care, and the extent and anatomic location of the trauma. Since the seriously wounded to killed ratio in Korea was 1:3 and in Vietnam was 1:6, Vietnam patients were more extensively and severely injured.[19] The incidence of 2.8% at Saint Paul Ramsey Hospital may represent an older and more severely injured patient.

From these figures, we can see that: (1) ARF with no other associated conditions and treated with dialysis is a relatively benign condition when treated appropriately, (2) rapid volume replacement with appropriate medical and surgical therapy has brought a marked reduction in the incidence of ARF, and (3) once ARF develops, the mortality remains high because of the seriousness of the associated injuries which produced the condition.

Pathology

The pathology seen in ARF is usually acute tubular necrosis. No correlation exists between the renal pathology and the clinical course. Glomeruli are usually normal. The tubules are usually dilated and contain casts. The peritubular cells may show swelling with epithelial injury and regeneration. Marked interstitial edema is usually present. Grossly the kidneys may be enlarged and swollen with a pale cortex and a congested medulla.

Etiology

Numerous theories have been proposed as to explain why ARF occurs. These include tubular

*Read at the Annual Orthopaedic and Trauma Seminar of the Hennepin County Medical Center, Minneapolis, Minnesota.

†From the Department of Surgery, Hennepin County Medical Center, Minneapolis, Minnesota.

obstruction, decreased glomerular filtration rate, renal interstitial edema, passive back diffusion of GFR, and increased cortical resistance. Decreased renal blood flow and increased vascular resistance seem to be uniformly present in acute renal failure.[4] Decreased renal blood flow and increased vascular resistance leads to cellular and tubular changes and the acutely irreversible state seen in ARF. Why the increased vascular resistance? Factors include renin and angiotensin, cellular edema with vascular obstruction, intravascular coagulation, arteriolar vasoconstriction and the prostaglandins.[5-8] Acute renal failure is produced by a series of complex and related factors, each of which is difficult to demonstrate individually.

Case Reports

Case 1

This 33-year-old man stopped to push his stalled car when another car struck him from the rear. The impact crushed both legs. When first seen, he had severe open distal femur fractures, grossly unstable knees, no popliteal or distal pulses with total anesthesia below both injuries. Xrays showed severe bilateral supracondylar femur fractures and a right fibular fracture. Both lacerated popliteal arteries were repaired at surgery, and his femurs were fixed with ASIF blade plates. There was no hypotension, and he had a good urine output during the procedure. He was started on Cephalothin and Gentamycin, and the wounds were closed three days after the initial debridements.

Shortly after the initial procedure he had an episode of oliguria. This responded to Mannitol and Furosemide. Over the next four days, he developed progressive oliguria and evidence of ARF, despite further medical treatment with Mannitol and Furosemide.

One week after admission, pseudomonas was cultured from his left leg. Two weeks following the injury, he developed massive rectal bleeding from a caecal stress ulcer requiring a right hemicolectomy and an ileal-transverse colostomy. Four days later, he required a left A-K amputation.

Dialysis cannulas were placed in his arm, and he was started on acute hemodialysis one week after injury. This was continued until seven weeks after injury when his renal function improved for dialysis to be discontinued.

One month after admission, he was explored following a wound dehiscence and found to have a large abscess from his previous surgery, and this was managed with an ileostomy. The Gentamycin which was stopped during his progression into acute renal failure was started at this time in addition to the Carbenicillin.

During the next three weeks he developed Candida septicemia and osteomyelitis in his right femur. Three months following injury, his blade plate was removed and a bone graft was performed. He was discharged to another institution for continuation of physical therapy to his right lower extremity. Seven months following injury, he had a normal creatinine clearance and was working on ambulation with crutches. He had diminished right knee motion with chronic pain and except for his left A-K amputation, had recovered satisfactorily.

Comment

Severe crush injuries, Gentamycin, and long surgical procedures were factors responsible for ARF in this patient. Stress ulcers which include caecal ulcers occurred in 19 out of 96 patients in ARF from Vietnam, 18 of these having clinically evident sepsis.[9] His protracted azotemic phase was related to his numerous surgical and septic complications requiring Gentamycin and Amphotericin for his Candida Sepsis. Wound dehiscence in Vietnam occurred in 22% of patients with ARF compared with the general surgical rate of 0.42%.[2]

Case 2

This 50-year-old man was on a night-on-the-town when he sustained an episode of micturition syncope while standing on the middle of the Ford bridge. He fell off the bridge to concrete pilings 100 feet below. Examination showed him to have a blood pressure of 60, deep facial lacerations, bilateral rib crepitus with a right flail chest, massive back and right soft tissue contusions, a right unstable iliac crest, and his left hip in external rotation. He was confused, but conscious.

His blood pressure responded to plasmanate, Ringer's Lactate and type specific blood. Xray showed an obscured aortic arch, fractured four through 12 ribs, fractured right scapula, right clavicle fracture, bilateral hemopneumothorax, and fractured left 8th and 9th ribs. Closed thoracostomy tubes were placed on the right.

Following detection of gross hematuria from catheterization, a cystogram showed no bladder rupture, and an infusion IVP showed a nonvisualizing left kidney. Pelvic Xrays showed a comminuted right iliac fracture, avulsion of the left greater trochanter, fractured lumbar one-five transverse processes with a wide diastasis and a comminuted L4 fracture. Because of a widened mediastinum and obscured aortic arch, an arch aortogram was performed. This showed no aortic rupture. During the procedure, he developed a massive increase in his right retroperitoneal hematoma. During surgery, a splenectomy was performed and a rent in the massive retroperitoneal hematoma closed.

A tracheostomy and radial artery cannulization were performed and he was placed in an anti-shock suit. Nineteen units of blood had been used prior to G-suit application, and five units of blood were required after application. Postoperatively, he showed evidence of "shock lung syndrome" and required PEEP and a volume respirator to maintain acceptable blood gases.

Two days following injury, his creatinine was 2.2 and his clearance 52 cc's. His urine output remained about 2000 ccs per day. He was started on Gentamycin in addition to Cephalothin for a right lower lobe pneumonia.

One week following injury, his BUN was 116 and his creatinine clearance was 16 ml per minute. At this time, hyperalimentation using essential amino acid solutions was started. Two weeks later his urine output increased to 500-1100 cc's per hour. His urine output gradually

diminished and one month following injury, his clearance was 101 cc's and his BUN 15 mg%. He was extubated three weeks following admission and shortly after this was transferred to the Orthopedic Service where he was placed in a hyperextension brace for his unstable lumbar fracture. Eight months later, he was ambulating with healing of all fractures.

Comment

ARF in this patient resulted from severe crush, hypotension, possibly type specific blood administration, and the use of Gentamycin. Pulmonary edema is frequent in non-oliguric renal failure due to non-recognition and was avoided here, although some element of fluid overload may have been responsible for the "shock lung" picture.[3] Urinary electrolytes must be monitored and replaced during the diuretic phase, during which sepsis is most common. Heparin therapy which was used in this patient may have been effective in avoiding the common occurrence of pulmonary embolism in the lengthy immobilized multiple fracture patient.

Case 3

This 10-year-old went to his garage to get his bicycle and was trapped between a fallen stack of trailer sidings and a car for almost twenty-one hours until being found the next morning. He was taken to the family doctor who administered fluids and transferred him to another local hospital. Initial examination showed his lower extremities to be deeply cyanotic and anesthetic from mid-thighs distally with no palpable pulses, massive edema, and bilateral foot drop. His blood pressure was 95/60 and his hemoglobin 20. He was given solutions of Methylprednisolone and 12.5 grams of Mannitol. Papaverine was injected into each femoral artery. Fasciotomies on both thighs and legs and bilateral sympathectomies were performed at surgery with the return of brisk bleeding.

During the procedure, his urine output was recorded at 200 ml. Postoperatively, he became hypotensive from fasciotomy bleeding and responded to blood and fluids. Shortly after, he became oliguric with 20 ml of urine being produced the next twelve hours. Mannitol and Furosemide were not used at this time.

He was seen the next morning by the Nephrology Service where attempted diuresis was unsuccessful. Laboratory showed a potassium of 7.5, BUN 63 mg%, creatinine 3.2, hemoglobin 14.7, and a serum osmolality of 296. He was administered insulin, dextrose 50, sodium bicarbonate, potassium exchange resins and dialyzed with a resultant lowering of his potassium.

Following this, he was transferred to Hennepin County Medical Center where hemodialysis cannulas were placed. He required transfusions for continued fasciotomy blood loss. Ten days post injury, he developed a pneumoperitoneum and a pyloric stress ulcer was plicated. He was started on hyperalimentation at this time. Two weeks following admission his fasciotomies were closed. Hemodialysis was continued for four weeks until his renal function had returned sufficiently.

Eight weeks following injury, bilateral transmetatarsal amputations were performed. Further skin grafting was performed to his fasciotomy sites, and two days later he underwent an emergency appendectomy for acute appendicitis. He recovered from the surgery uneventfully and three and one half months following injury, was walking and returned home. His creatinine clearance showed a corrected value of 102 cc's per minute.

Comment

This case illustrates the effects of dehydration, crush, hypotension, and possibly unattempted early diuresis in the pathogenesis of ARF. Early dialysis, young age, recognition and management of associated medical and surgical problems and the avoidance of infection led to complete recovery. The use of Mannitol and Furosemide and increased fluids may have prevented ARF.

Case 4

This 33-year-old diabetic was pinned between a grader blade and another industrial vehicle, sustaining a fractured pelvis and crush injuries to both legs from mid-thigh distally. He was taken to a local hospital where, because of an absent left popliteal pulse, his left femoral artery was explored and repaired with an autologus saphenous skin graft. He was then transferred to another larger hospital where he underwent an exploratory laparotomy and was found to have a large retroperitoneal hematoma. Postoperatively, he developed a blood pressure between 0 and 60 to 70 systolic over an eight-hour period due to massive retroperitoneal bleeding.

Shortly thereafter, he developed oliguria with progressive azotemia and a rising serum creatinine. Three days following injury, arrangements were made for transportation to Hennepin County Medical Center. Attempts to achieve diuresis with Furosemide prior to transfer were unsuccessful, and he was given a potassium exchange resin for a serum potassium of 7.7. After a four hour ambulance trip, he presented in our Emergency Room with agonal respirations, an electrocardiogram showing widened QRS complexes and frequent premature ventricular contractions. His serum potassium at this time was 9.4 mg%. He was immediately intubated and given sodium bicarbonate, calcium gluconate, dextrose 50, and insulin I.V. with a return to normal and his electrocardiogram and a subsequent lowering of his serum potassium. He was found to have disseminated intervascular coagulation and was given fresh frozen plasma. He was taken to the operating room where a dialysis cannula was inserted and shortly thereafter, he was hemodialyzed with a further lowering of his serum potassium. After he was sufficiently stabilized, he underwent a below the knee amputation for a grossly necrotic left lower extremity.

During the next eleven days, he improved with healing of his left stump and his lower extremity. Hyperalimentation was instituted. He was gradually weaned from the respirator. Eleven days after transfer he became depressed with progressive obtundation. Brain scans, lumbar puncture, and left carotid angiogram were undiagnostic for a suspected fungal meningitis. Because of progressive neurologic deterioration, Intrathecal Amphotericin B was added to his systemic Amphotericin. Despite all medical therapy, he sustained a cardio-respiratory arrest 24 days after injury and died. An autopsy was not performed.

Comment

This case illustrates the effects of a severe crush injury

and profound hypotension from a retroperitoneal hemorrhage in producing ARF. Hyperkalemia can become manifested very quickly in a post-traumatic hypercatabolic patient and its unrecognition or lack of prevention can become fatal. Medical management can usually prevent this complication until hemodialysis can be performed. Despite marked improvement, this patient probably died from sepsis, the leading cause of death in ARF. A prolonged course of Cephalothin may have contributed to his sepsis.

Case 5

This 63-year-old male was adjusting a new corn seeder when a 2,000 pound lift fell on his left iliac crest. He was taken to his family doctor where an I.V. was started and he was transferred to a larger medical center because of a suspected pelvic fracture. Xrays at this hospital showed a double vertical severely displaced pelvic fracture. Because of gross hematuria, a cystogram was performed which showed a large extraperitoneal rupture of the bladder. An urologist treated this bladder rupture with catheter drainage. A Steinmann pin was then placed in his proximal tibia, and he was placed in traction for his pelvic fracture.

The day following admission, an nasogastric tube was placed because of abdominal distention. Throughout the next week, this ileus persisted with the patient complaining of periodic diffuse abdominal pain with associated fever. One week following admission, a film of his pelvis showed some free air outlining his large bowel. An abdominal film showed massive pneumoperitoneum. He was taken to surgery later that day where a transection of the sigmoid colon was found. Both ends were lying free in the pelvis and a diverting colostomy with a distal Hartmann's pouch was performed.

Postoperatively, the patient had a hypotensive episode which responded to fluids. One week postoperatively, a delayed primary closure was performed. Two days following this, he developed an upper gastrointestinal bleeding with a four-hour period of hypotension which eventually responded to blood replacement. During the next three days, he required 14 units of blood and during this period developed progressive oliguria with a response to Furosemide. Two weeks postoperatively, his creatinine clearance was 2 cc's per minute, his BUN 99 mg%, and his urine output was about 1,000 ml per day. He was transferred to Hennepin County Medical Center after receiving two units of packed cells. On arrival he was comatose with Cheyne-Stokes respirations. Pus was exuding from his drain site. His potassium was 5.5, and his BUN was greater than 100. His hemoglobin was 8.5, p02 was 39, and his PCO_2 was 37. He was intubated and placed on a respirator. Hemodialysis cannulas were inserted and he was started on hemodialysis. His gastrointestinal bleeding increased. Emergency endoscopy was performed, and because of the extent of the bleeding, we were unable to locate a specific part of the stomach where the hemorrhage was occurring. Following this, transfemoral celiac angiography was performed using selective Pitressin infusion to stop the bleeding. This produced a ventricular fibrillation which converted with counter-shock. His bleeding continued, and massive blood replacement was continued for 24 hours. At this time, intergastric Levophed, in addition to large amounts of fresh frozen plasma, were successful in stopping the bleeding.

Following hemodialysis, he was taken to surgery where the findings included an abscess cavity draining from an open Hartmann's pouch. This was repaired and he was drained extensively. His bleeding ceased postoperatively. Daily dialysis corrected his massive 50 pound fluid overload, and he gradually became able to respond and to sit up in a chair.

However, he became more jaundiced with symptoms of liver failure. Twelve days after his admission, his Bilirubin was 14.1, and one week later, it had increased to 44. He had initially been started on hyperalimentation which was continued throughout his hospital course. He was gradually able to be weaned off the respirator.

During his progression into liver failure, his acute renal failure progressed from non-oliguric renal failure to oliguric renal failure. Renograms at both times showed bilateral function with no excretion. A liver scan was compatible with diffuse liver disease. His wounds healed and his drains were discontinued. However, six weeks following admission he again had massive upper gastrointestinal bleeding on dialysis with hypotension which required Levophed. He died one week later of pneumonia and secondary gram negative sepsis. Autopsy showed bilateral acute tubularnecrosis, gastric and pyloric channel stress ulcers, pneumonia, retroperitoneal hematoma, and a pelvic abscess.

Comment

This case illustrates the effects of crush, hypotension, unrecognized sepsis, stress ulcers, hypotension, and Gentamycin in producing ARF. This illustrates, again, the importance of avoiding sepsis in preventing stress ulcer bleeding. Jaundice, sepsis, and late oliguria are poor prognostic signs in ARF.[2]

Analysis of Case Presentations

All five patients sustained crush injuries, and all were hypotensive at some time during their hospital course. Gentamycin in three patients, blood transfusions in one patient, may have contributed to renal failure. Four patients required respiratory support. Stress ulcers developed in three patients as did sepsis. Early severe hyperkalemia occurred in two patients, and liver failure, wound dehiscence, and appendicitis in one. Three patients presented with normal urine volumes with late oliguria occurring in two of these patients. Two patients died and the other three patients showed a normal return of renal function.

Mannitol and Furosemide

The two drugs important in preventing ARF are Mannitol and Furosemide. Mannitol has routinely been used in the military for this purpose.

Mannitol is a reduced form of manose and is distributed in the extracellular compartment. It is freely filtered in the glomeruli with no tubular reabsorption. Its value in preventing ARF may be in preventing afferent arterior or vasoconstriction and peritubular cellular edema and in maintaining high tubular flows to prevent cast precipitation.[10] It has limited value in anuric states and must be given cautiously in patients prone to develop congestive heart failure due to its effect on increasing intravascular volume.

Furosemide is a potent diuretic which may be effective with low or absent glomerular filtration rates. Its value in preventing ARF lies in its lowering of renal vascular resistance and increase in renal blood flow.[11] It is safe, but must be given cautiously due to occasional reports of ototoxicity.

Managing Trauma

To prevent ARF in trauma patients, one must support intravascular volume, maintain urine volume, eliminate obstructive factors, and follow base line laboratory values. Blood pressure and intravascular volume may require a central venous pressure line, large amounts of fluids and occasional use of an anti-gravity shock device.

Urine output should be measured with a bladder catheter with hourly urine volumes. Bladder rupture must be ruled-out early. If oliguria or anuria is diagnosed, hydration must be pursued and Mannitol and Furosemide used appropriately. Furosemide should be used to initiate urine volume after appropriate fluids have been given. Furosemide, Mannitol, and fluids should be given to sustain urine output at 60-100 ml per hour.

In a study of ARF from Vietnam, 42% presented with normal urine volumes so that serial creatinine and BUN values must be followed.[2] The mortality of non-oliguric (high output failure) appears to be significantly lower in this series (62-40%.) This is related to better nutrition and fluid balance, fewer electrolyte problems, and avoiding the need for dialysis.

Diuresis should be attempted in all patients with anuria. Investigators have suggested a period of functional renal failure which can be reversed with Mannitol and Lasix.[10] Prevention of ARF in the surgical patient requires preoperative hydration and diuresis and the use of judicious amounts of Furosemide and Mannitol during surgery to maintain diuresis. Caution must be used in interpreting creatinine and BUN values as significant rises in serum creatinine only occur with 30 or 40% of renal function remaining. The BUN is influenced by numerous extra renal factors and must cautiously be interpreted. The creatinine clearance presents a better clinical estimation of renal function.

Causes

Patients presenting with acute renal failure usually have no one common cause as seen in Table 1. Hypotension usually on a hypovolemic, but occasionally on a septic or cardiogenic basis, is usually present. Transfusion reactions are often

TABLE 1

Precursors to Acute Renal Failure[1,2,3]

1. Trauma
   - Shock
   - Crush Syndrome
2. Disease
   - Septic Shock
   - Hemolysis (2° Clostridium Infection)
   - Peritonitis (Septic) (Chemical)
   - Pancreatitis
   - Immunologic Reaction (Mismatched Blood)
   - Disseminated Intravascular Coagulopathy
3. Medications
   - Nephrotoxic Antibiotics
   - Tetracyclines
   - Kanamycin
   - Neomycin
   - Gentamycin
   - Cephalothin
   - Loridine
   - Methicillin
   - Amphoterocin B
   - Colistin
   - Streptomycin
   - Sulfonamides
   - Vancomycin
   - Penicillin
   - Bacitracin
   - Polymixin

   Others
   - Anesthesia (In General)
   - L.M.D
   - Epsilon Amino Caproic Acid
   - Methoxyflurane
   - Vasoconstrictors
   - Acetazolamide (Diamox)
   - Aspirin
   - Dicumarol
   - Diuril
   - Dilantin
   - Horse Serum
   - Ferrous Sulfate
   - Apresoline
   - Phenacetin
   - Vitamin D
   - Butazoladine
4. Fluid and Electrolyte Problems
   - G.I. Tract Fluid Loss Without Adequate Replacement
   - Systematic Dehydration for Tests
   - N.P.O. Without Adequate Fluid Intake
   - Hypokalemia
5. Obstruction
   - Renal Vessels
   - Ureters
   - Urethra
6. Cardiopulmonary Bypass

difficult to implicate, but are frequently contributory. Non-oliguric renal failure may occur more frequently in cases with transfusion reactions.[12] Experimental crush injuries with myoglobinuria and hemolysis secondary to burns have produced ARF in animals. Seizures, coma, strenuous exercises, and viral illnesses produced acute non-traumatic rhabdomyolysis which was the sole identifiable factor in the production of ARF in fifteen patients.[13] A large percentage of ARF in the trauma patient is preceded by a crush injury.

Sepsis

Sepsis is a serious problem in the multiple trauma patient, and the use of aminoglycosides such as Gentamycin often are an exacerbating factor. Gentamycin should be administered with a dosage schedule as determined by the creatinine or creatinine clearances. These tests need to be followed closely. Kanamycin, Cephalothin, Cephaloridine, Vancomycin, and Tetracyclines are other examples of antibiotics which need to be avoided or dosages adjusted in ARF.

Baseline Serum Values

After renal failure has been established, base line serum tests should be measured (Table 2). Urinary tract workup should be performed to exclude renal, bladder, and urethral trauma. An infusion IVP may give clues to pre-existant or new renal disease. A renogram may predict return of renal function. An arteriogram may occasionally be indicated in trauma. Serum creatinine, BUN, phosphorus, electrolytes, and uric acid must be followed and controlled. Urinary sodium values should be drawn. A sodium of 20 mEq per liter may point to prerenal causes or be found in non-oliguric ARF. A high urinary sodium is usually a poor sign of early recovery.

Hyperkalemia

The most serious early complication is hyperkalemia. This may appear quickly (Table 3). Hyperkalemia can usually be controlled with calcium salts, dextrose and insulin, potassium ion exchange resins, and avoiding potassium administration until dialysis can be instituted. Fluid overload with secondary hypertension must be avoided. It is important to realize that non-oliguric renal failure patients have a limited ability to excrete sodium and fluids must be watched very carefully.

TABLE 2
Management of Decreased Urine Output[1]

I. Check Drainage System
- Patient
- Nurse
- Rule Out Post Renal Problem (Ureters to Chart)

II. Evaluate Intravascular Volume
- Blood Pressure
- Pulse
- Central Venous Pressure
- Pulmonary Wedge Pressure

III. Studies
- Blood or Serum
  - Electrolytes
  - B.U.N.
  - Creatinine
  - Uric Acid
  - Coagulation Studies
- Serum and Urine Osmolarities
- Urinalysis
- Renogram
- Arteriogram
- Biopsy (Rarely)

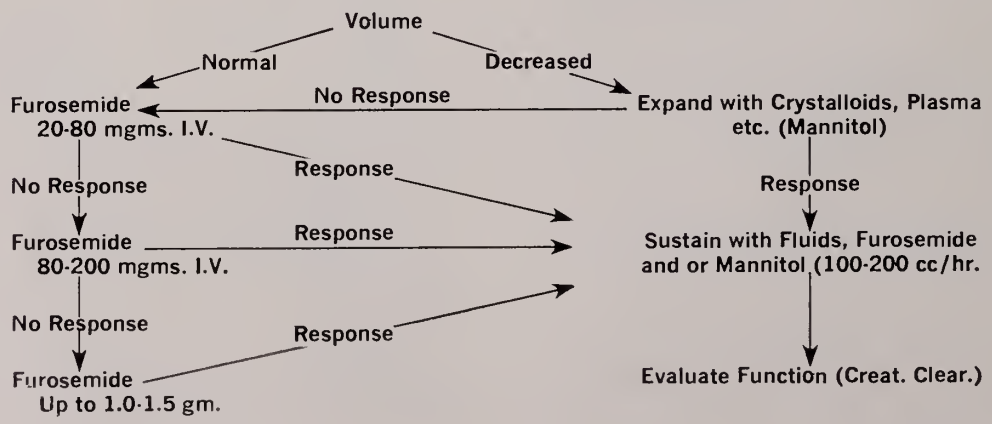


TABLE 3
Management of Hyperkalemia

I. Rapid Response (5 Min. to 120+ Min.)
   - Calcium Solutions I.V. (Balances K+)
   - Sodium Bicarbonate Solutions I.V. (Displaced K+ Intracellularly)

II. Delayed Response (30 Min. to 24 Hrs.)
   - Insulin Plus Glucose (1 to 3 Ratio) (Displaces K+ Intracellularly)

III. Longer Delay in Response (30 Min. to As Long as Continued)
   - Nasogastric Suction (Removes K+ and H+)
   - Kayexalate (30 to 100 gm.) (Removes K+)
   - Dialysis (Removes K+)
     - Peritoneal
     - Hemo

IV. Don't Give K+ Containing Solutions.

Exercise Care in K+ Reduction in Digitalized or Dig-Toxic Patient

Respiratory Insufficiency

Twelve patients in a series which represented 83% of ARF patients from Vietnam were found when initially seen to have respiratory insufficiency. Ten of these patients had p02 values less than 50 and five of these patients had non-oliguric renal failure. All patients had normal CVP values. Etiologies were felt secondary to contusion, sepsis, shock, fat emboli, CHF and oxygen toxicity. These authors felt this problem could be prevented by: (1) avoidance of excessive use of crystalloids, (2) recognition of non-oliguria ARF and (3) understanding of CVP. All patients improved with dialysis.[14] Digitalization may be required, the dose being adjusted according to renal function. Later complications include sepsis, nutrition, stress ulcers, and dialysis complications. Judicious use of antibiotics must be implemented. Evidence, although not conclusive, has shown a decreased white cell phagocytosis and a decreased delayed sensitivity response in patients with ARF.[16] Wounds and abscesses must be managed and urinary tract infections avoided.

Studies have shown an improved survival of patients receiving hyperalimentation using essential amino acids and dextrose administration.[15] These solutions contribute to an anabolic state associated with protein synthesis, decreased cellular breakdown and the intracellular accumulation of potassium associated with cellular synthesis. This may lead to a decreased catabolic and secondary azotemic phase, an increased resistance to infections and the avoidance of hyperkalemia, all of which may contribute to a decreased mortality in ARF.

Dialysis access presents an occasional problem and heparinization may precipitate gastrointestinal bleeding. Peritoneal dialysis can be occasionally used, but not effectively in the post-laparotomy surgical patient. Prophylactic dialysis presents the complications of uremia, i.e. mental confusion, pericarditis, gastrointestinal symptoms, and bleeding. Its role in the improvement of mortality seems beneficial.[17]

Death in ARF is usually related to sepsis and hemorrhage. Age and the severity of the underlying problems play an important part in the prediction of mortality. The usual duration of the azotemic phase usually lasts about two weeks, but usually increases as complications occur. The complications in the diuretic phase include sepsis and electrolyte problems. Studies have shown a nearly complete recovery from acute tubular necrosis, but often with some subclinical existing renal impairment.[18]

Summary

Five patients seen over a 12 month period have been presented either primarily treated, seen, or referred to Hennepin County Medical Center, and their cases have been discussed regarding the etiologies, management and possible prevention of ARF. Clearly, if a reduction in incidence and mortality is to be achieved in ARF, clinicians must be aware of the resources available and the prevention and management of ARF.

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10-18. Will be found on page 543.

Spinal Injuries in a Multiple Trauma Patient*

GARY WYARD, M.D.† and DAVID BRADFORD, M.D.‡

An analysis of 188 patients with spinal injuries treated at Hennepin County Medical Center between 1969 and 1974 was done with special regard to the types and frequency of associated injuries. A discussion of major problems in diagnosis and management of spinal injury patients in the multiply injured patient following similar reviews in the literature are presented.

THE PURPOSE OF THIS study is to review our experience with spinal injuries and define specific problems of diagnosis and management in spinal injuries with associated multiple injuries.

The problem of spinal cord injuries is a serious one. There are about 100,000 patients in the United States with permanent paralysis secondary to injuries of the spinal cord. Each year about thirty-five patients per million population (about 10,000 new patients per year) are added to the spinal cord injury total in the United States.[2]

Cheshire, Director, Spinal Injuries Center, Victoria, Australia, stated in 1971 that people treating spinal cord injuries must recognize that the next major problem which is coming upon us is the acute management of the patient with spinal paralysis and severe associated multiple injuries.[3]

Spinal injuries in the multiple injured patient range over a wide spectrum. The problem is becoming increasingly more important because of the upward trend in motor vehicle accidents, the skill and speed with which the severely injured are transported and advances in resuscitation. The high mortality associated with abdominal, thoracic, and cranial injuries is well recognized.

When these injuries are associated with spinal column and spinal cord injuries, the problems are compounded. It is the various combinations of paralysis, loss of pain sensation, alterations of reflexes and autonomic dysfunction that present potential problems in the diagnosis and management of associated injuries.

There has been little in the literature concerning the frequency and management of spinal injuries in the multiply injured patient. Pitt and Shannon[1] in 1970 published an article on spinal injuries in the multiply injured patient. Bricker and others in 1971 reported on eighteen patients with major injuries to the chest, thoracic outlet and abdomen with spinal cord injury.[4] Most studies of frequency and treatment of spinal injuries with other associated injuries come from spinal cord injury centers in other countries. McSweeny, Spinal Injuries Unit, Oswestry, gave a paper on the early management of associated injuries in the presence of coincident damage to the spinal cord.[5]

Accurate diagnosis in injury to the spine is essential in order to provide appropriate treatment not only of the spinal injury, but also injuries sustained by the patient. The surgeon, bearing the primary responsibility for overall management, must be aware of the unusual problems which may manifest in patients who have sustained multiple trauma who are not neurologically intact.

Clinical Material

One hundred eighty-eight traumatic spinal injuries seen at this hospital between 1969 and 1974 were reviewed.

Lesions were classified as stable and non-stable based on the classification of Holdsworth.[6] Forty-one of the lesions were unstable, the remaining were classified as stable. There were thirty-one patients with neurological deficits and 157 without neurologic findings. The level of osseous injury was also determined.

TABLE 1
Classification (Stable vs. Unstable)

Stable	147
Unstable	41

*Read at the Annual Orthopaedic and Trauma Seminar of the Hennepin County Medical Center, Minneapolis, Minnesota.

†Orthopaedic Resident, University of Minnesota, Minneapolis.
‡Associate Professor of Orthopaedic Surgery, University of Minnesota, Minneapolis.

TABLE 2
Classification (Osseous Injury and Dislocations with Neurological Deficit)

	Incomplete	Complete
Cervical	10	5
Thoraco-lumbar	10	6

TABLE 3
Classification (Osseous Injury and Dislocation Without Neurological Deficit)

Cervical	36
Thoracic	41
Lumbar	87

TABLE 4
Classification (level)

C1-C2	28
C3-C7	22
T1-T10	28
T11-L1	57
L2-L5	50

Associated Injuries

There was a high incidence of associated injuries excluding abrasions, lacerations and contusions.

There were sixty-five patients of the 188 with at least one major associated injury. In the thirty-one patients with neurological deficits almost half had had an associated injury (fourteen patients.)

Guttman (1963) reported associated injuries in 28% of 386 patients with traumatic paraplegia and quadriplegia.[7] Harris (1968) found about 50% of cervical spinal cord injuries had associated injuries.[8] On a review of 595 paraplegics treated in Germany, Meinecke found 51% with associated injuries.[9]

TABLE 5
Associated Injuries

Head:	
Concussion	28
Fractured Skull	6
Fractured Mandible	5
Fractured Larynx	1
Chest:	
Fractured Ribs	14
Shoulder Injuries	14
Hemothorax & Pneumothorax	12
Fractured Sternum	2
Contused Lungs	2
Upper Extremity Fractures	14
Lower Extremity Fractures	20
Abdomen—Pelvis:	
Fractured Pelvis	11
Contused Kidneys & Ruptured Bladder	8
Ruptured Spleen	7
Lacerated Liver	4
Fractured Acetabulum	4
Small Bowel Laceration	1

Etiology

A history of trauma was obtained in all cases. Falls from heights were the most common cause of injury. Motor vehicle accidents were the second most common cause. Sporting accidents, assaults, gunshot wounds were also reasons for injuries. Of these with neurological deficits, motor vehicle accidents were the most common cause by far and accounted for fifteen of thirty-one patients.

TABLE 6
Etiology of Spinal Injuries

All Injuries:	
Falls	76
Motor Vehicle Accidents	45
Assault	8
Motorcycle	7
Pedestrian	6
Gunshot Wounds	5
Sports:	
Toboggan	2
Diving	1
Horseback Riding	1
Trapeze	1
Water Skiing	1

TABLE 7
Injuries with Neurological Involvement

Motor Vehicle Accidents	15
Falls	7
Assault	4
Gunshot Wounds	3
Toboggan	2

Initial Management

From the onset three major points of concern in management are: (1) stability of vertebral column and its potential for becoming painless and structurally sound, (2) preservation and/or restoration of the functional integrity of the neural contents, and (3) diagnosis and management of other life threatening injuries.

Fortunately, not all fracture or fracture dislocations are accompanied by spinal cord or nerve root injury. However, in the patient with an unrecognized or unconfirmed spinal injury, early handling may convert a normally functioning or mildly injured neural system into a severely paralyzed one. A major principle in post-trauma injury when the circumstances might suggest injury to the spine is stabilization during transportation and prompt treatment of other life threatening injuries. Patients should be examined "in situ" for pain and tenderness of the spine, for increase separation of palpable spinous processes and for impaired neural function. The presence of any of these dictates careful immobilization of the spinal column on a spinal board.

Initial neurologic examination with special attention to main muscle groups, sensation levels, deep tendon reflexes, Babinski, cremasteric, anal

response and bulbocavernosus reflexes are essential. From such information, one can determine complete from incomplete lesions as well as the most appropriate method of management.

Neurological Consequences of Trauma to the Spine

Spinal shock deserves consideration when evaluating multiple trauma patients with transected cords. This is a state that follows spinal cord transection whereby muscles below the lesion are flaccid and paralyzed, and reflexes are lost. Sensation is absent and tonic vasomotor responses are lost. This state may add confusion to both diagnosis and management. Similarly, when there is interference with vasomotor control in spinal injuries above the sympathetic outflow at the mid-thorax level causing a decrease in sympathetic tone and resulting fall in blood pressure, the massive transfusion required in multiple injuries is compromised. Fluid overload and pulmonary edema are easily produced.

Head Injuries

Henry Bohlman has reported on the high incidence of head and neck injuries.[10] He reported on 50 patients who died of automobile accidents and noted a 60% correlation between brain and cervical cord injuries. Phillip Harris found head injuries the most common associated injury in traumatic paraplegia and quadriplegia.[8]

Of our 31 patients with neurologic deficits due to cord injury, seven had head injuries. As noted, 60% of the cervical spine fractures had head injuries. These associated injuries present peculiar problems of diagnosis and management. In the unconscious patient, fractures of the spine are easily missed. Xrays of the cervical spine should always be obtained first and then skull Xrays after cervical injury has been determined.

Chest Injuries

In patients with thoracic and lumbar spine injuries associated chest trauma is common, but is not as critical as in cervical spine lesions. In cervical cord injuries, with associated paralysis of accessory muscles of respiration, the patient is totally dependent upon the diaphragm for breathing. Tracheostomy is vital. Injuries to the diaphragm, heart, and other mediastinal structures must be considered. Hemorrhage from the thoracic cavity is less well tolerated by the patient with cord injury and early thoracotomy is the rule when indicated.[4] In the patient with minimal or no neurological deficit, complications are related to movement and positioning so that a neurologic catastrophy does not occur. When a pneumothorax or hemothorax is present appropriate chest tubes should be placed.

Abdominal Injuries

Abdominal injuries are easily missed in the spinal injury patient. Loss of pain sensation can mask a ruptured viscus or permit peritonitis to go unrecognized. The flaccidity seen in the acute phases of spinal shock permits the abdomen to be soft when under certain circumstances it would normally show rigidity. A distended abdomen was found to be a confusing feature in the patients reviewed in this study since ileus from spinal injuries resemble ileus from other injuries. Abdominal rigidity associated with fractures of the lumbar spine and incomplete lesions may suggest intra-abdominal injury when none is present. Local bruising together with history and appropriate x-rays give the most helpful clues. At this hospital and from other reported reviews, abdominal tap and aggressive laparotomy is recommended over watchful worry when associated intra-abdominal injury is suspected.

Extremity Injuries

A major vascular injury or fracture may be present within an area of anesthesia. In the paralyzed limb, fractures occur quite often and their treatment requires special measures to avoid pressure sores, contractures and stiffening of joints. Compound fractures should be debrided and irrigated as soon as general conditions permit. Uncomplicated dislocations are gently reduced. Fractures are easily reduced and splinted. In paralyzed extremity fractures as a general rule, circular casts should not be applied. Pillow splints or open bivalved, well padded casts changed every several hours are adequate. If fracture reduction is difficult to hold, open reduction and internal fixation are indicated when the patient's general condition is stabilized. Fractures or paralyzed limbs normally heal even with little immobilization. It is not advisable, however, to accept gross angular deformity in the anesthetic limb because of the difficulties involved in fitting of appliances.

Consideration for Spinal Surgery and Management

Spinal injuries are treated differently by many Neurosurgeons and Orthopedists and it is beyond the scope of this paper to review this controversial topic. Anatomical reduction of the bony injury should be accomplished early and is often the best decompression of neural structures.

The nature of each injury will dictate the specific means of reduction (operative vs. non-operative.) Operations for decompression should be directed to the area of compression. The bony compression of the neural elements lies anterior. Hence, the routine laminectomy no matter how wide or extensive, rarely if ever, provides decompression. We feel its use in these cases as a sole method of decompression is therefore to be condemned.

On the other hand, anterior decompression attacks the site of involvement and may result in improved neurological function in incomplete lesions as long as a year post injury. Anatomical reduction by Harrington rod instrumentation and spine fusion has recently been shown to promote early rehabilitation and prevent delayed complications of pain and instability in thoracolumbar and lumbar injuries.[13]

Surgical procedures done to debride open wounds, remove intraspinal bone fragments, and remove local neural compression are generally accepted by everyone. However, the treatment of the majority of spinal injuries is not so obvious. Only when partial spinal neural loss and axial compression co-exist, can surgical decompression be expected to help. Major treatment failures are related to blunt traumatic lesions with immediate and total sensory motor loss below the injured level. In this group, patients rarely recover any neural function in spite of all available types of treatment.

Conclusion

The basic management of the spine does not change in the multiple injured patient. Maintenance of an airway and ventilation remains the primary goal, but immobilization of the spine and reduction of fracture dislocations are of primary importance. In multiple injured patients a high index of suspicion is necessary to rule-out spine injury. Emergency care must be directed toward preservation of life without further insulting the neurological status of the patient.

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Value of the Counterpressure Suit (M.A.S.T.) in Pre-hospital Care

G. PATRICK LILJA, M.D.;* DARYL J. BATALDEN, M.D.;* BRUCE E. ADAMS, M.D.;* ROBERT S. LONG, M.D.* and ERNEST RUIZ, M.D.*

Three patients with severe traumatic blood loss were resuscitated with the aid of the pressure suit. The rationale for use of this device is discussed.

THE NUMBER ONE cause of death between 0 and 40 years of age in the United States is trauma. There is evidence that one of the major causes of death from trauma is inadequate care from the scene en route to the hospital.[1] Another cause is delay in treatment because of transportation time to get definitive medical care. When there is a delay in early care or when transportation time is long exsanguination may occur. Conversely, when early care results in the reversal of shock and control of hemorrhage death may be prevented.

In 1903, Crile[3] demonstrated that external counterpressure applied circumferentially around the body was effective in controlling hemorrhage and hypotension. A study by Batalden et al.[2] has shown that external counterpressure in the form of an inflatable blanket can successfully control hemorrhagic shock in patients with severe pelvic fractures who have been hospitalized. Recently a device which is similar to the wrap around inflatable blanket "G suit" has been developed which can be applied at the scene by trained emergency personnel. This device is called the Pneumatic Trousers (Military Anti-Shock Trousers) or MAST. This garment applied circumferential pressure around the body below the diaphragm. Applied in this manner it may:

a. Control or stop internal bleeding;
b. Transfer blood from the lower part of the body to vital organs in the upper part; and
c. Stabilize fractures of the pelvis and lower extremities.

One study (Kaplan, Civetta, Nagel, et al)[5] has shown that this garment is suited for civilian use. They believe that the reduction in bleeding and autotransfusion from the lower part of the body allows for more time in transportation and preparation for surgery.

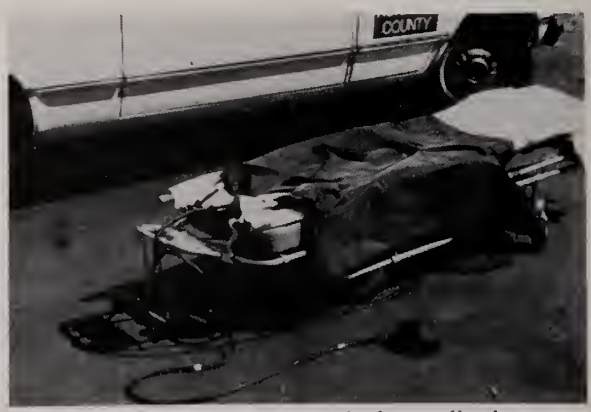


Fig. 1—M.A.S.T. trousers ready for application.



Fig. 2—M.A.S.T. trousers applied and inflated.

*Departments of Emergency Medicine and Surgery, Hennepin County Medical Center, and the Minneapolis Medical Research Foundation, Inc., Fifth and Portland South, Minneapolis, Minnesota.

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Indications for Use

The MAST is applied at the scene of the accident by ambulance or rescue personnel when indications of shock secondary to trauma exist. In addition, our initial experience indicates that it may be useful in other forms of shock as well. According to our current protocol ambulance personnel should apply the trousers when a patient has a systolic blood pressure of less than 90 with suspected trauma. In addition it is useful for shock from other causes such as ruptured abdominal aneurysm or any form of hypovolemic or stagnate shock. The trousers are contraindicated where there is isolated intracranial damage. In addition, we do not currently use it for suspected cardiogenic shock or in patients with congestive heart failure. The garment (Figures 1 and 2) is relatively easy to apply by ambulance or rescue personnel and requires approximately 60 seconds to fully inflate. Once applied, the trousers should be left on until the patient reaches a medical facility where definitive medical care is available. It should not be deflated until intravenous fluids can be given, blood is available and surgical teams are ready. The most frequent problem we have experienced is an urge to quickly deflate the trousers for wound exposure before adequate preparations have been made. Xrays can be taken through the garment and a Foley catheter can be inserted between the legs. In addition, a new model of the MAST trousers has been developed in which the body compartment and each leg compartment can be inflated and deflated independent of the other. This allows for exploration of wounds in each of the three areas without total loss of compression.

Case Reports

We began using the MAST suit with our ambulance personnel in February 1974. The Table summarizes the data obtained in cases so far. In addition, three brief summaries are presented to further demonstrate its applicability.

Case 1

A 20-year-old male sustained a gunshot wound to the left buttock. When seen by the ambulance crew he appeared pale and in shock. No blood pressure was obtainable at the scene. A MAST suit was applied and a blood pressure was taken by the ambulance crew which then recorded at 80/0 mm Hg. This later came up to 130 mm Hg systolic with the administration of three liters of Ringer's lactate and four units of plasma in the emergency department. On exploration in the operating room the patient was found to have sustained a laceration of the left internal iliac artery, laceration of the external iliac vein, and small bowel perforations. Also, a fragment went through the left arm resulting in an open fracture of the left ulna. The patient subsequently made an uneventful recovery.

Case 2

The second patient is a 28-year-old male who sustained a gunshot wound to the left chest. Blood pressure was unobtainable at the scene. A MAST suit was applied and an I.V. of Ringer's lactate, 500 ml was administered while transporting from the scene to the hospital. Blood pressure on arrival was 55 mm Hg. In the Emergency Department two liters of Ringer's lactate, 500 ml of plasma, and 1500 ml of type specific blood were given resulting in an increase in blood pressure to 120 mm Hg. At this time an attempt was made to lower the pressure in the G suit and the blood pressure immediately fell to 90 mm Hg systolic. The trousers were reinflated and the pressure immediately rose to 110 mm Hg. Operating teams were readied and on surgical exploration the individual was found to have suffered a left hemothorax, a hole in the diaphragm, a ruptured spleen and an amputation of the tail of the pancreas as well as small bowel perforations. The patient has now recovered and is back to his normal state.

Case 3

The patient was a 52-year-old male who struck a tree while driving a panel truck. The patient was pinned in the wreckage for a significant period of time and when extricated his blood pressure was unobtainable. The MAST suit was applied and a blood pressure of 80 mm Hg was obtained. The patient received one liter of Ringer's lactate while being transported in the ambulance. Three liters of Ringer's lactate and 750 ml of plasma were administered in the Emergency Department. The patient was taken to the operating room after bilateral chest tubes had been placed. An attempt was made to deflate the trousers but the patient's blood pressure began dropping. The patient was therefore placed on the operating table after the surgical team was completely ready. The G suit was slowly removed but almost immediately the patient suffered a cardiac arrest necessitating closed chest heart massage and immediate entry into the abdomen to control bleeding by gaining control of the aorta. In surgery the following conditions were found; complete avulsion of the spleen, several small lacerations of the liver, avulsion of the tail of the pancreas and numerous mesenteric bleeders and a rupture of the hepatoduodenal ligament. The patient, during surgery, received 22 units of blood, two units of fresh frozen plasma, and eight units of platelets. The patient had a rather stormy postoperative course but was eventually discharged 120 days after admission.

Discussion

Our experience with the counterpressure "G suit" indicates to us that it is an extremely valuable adjunct in dealing with severe trauma. We feel that it has a definite place in the on-the-scene management of hypovolemic shock and in subsequent management in the hospital. Also, our

initial experience does not substantiate the allegation that the G suit is contraindicated in the presence of chest trauma. We feel the effect of transfusing blood from the lower extremities to the central circulation is valuable in bleeding above the diaphragm as well as below. A study by Espinosa[4] indicates a decrease in respiratory excursion or a decrease in vital capacity with G suit application. This has so far proved to be of no consequence in our experience. However, we are alert to this possible problem and are careful to see that the patient receives positive ventilatory support during the entire time that the suit is inflated.

We believe that our short experience with the anti-shock trousers has more than demonstrated its usefulness. We feel that it has prevented the deaths of patients in at least three cases. Furthermore, its ease of application by trained rescue personnel makes it uniquely suited for widespread use

TABLE
Use of M.A.S.T. In Pre-Hospital Care of Patients

Case	Age	Injury	BP at Scene	BP in G Suit	Fluids Used	Outcome
1	20	Gunshot wound lt buttock with laceration ext iliac vein and int iliac artery	Unobtainable	80 130	Ringers 4 liters Plasma 10 units Whole blood 13 units Packed cells 3 units	Discharged A & W in 10 days
2	28	Gunshot wound lt chest, abdomen & arm resulting in rupt. spleen, amputation tail of pancreas, multiple small bowel & colon perforations, shattered rib, hemothorax	Unobtainable	50 120	Ringers 6 liters Plasma 2 units Blood 6 units	Discharged
3	52	Auto accident with resulting rupt. spleen, liver laceration, avulsion tail of pancreas, ruptured hepato-duodenal ligament & multiple mesenteric bleeders	Unobtainable	80 (When suit removed arrested)	Ringers 4 liters Plasma 3 units Whole blood 22 units Platelets 8 units Fresh frozen packed cells 2 units	Discharged after 142 days
4	60	Auto accident with resulting fractured pelvis and bilateral fractured ribs 2-9.	Not taken. BP in ER 80 systolic & suit then applied in ER.	110/80. Suit deflated with fall to 94/60. Suit reinflated with rise to 110/70.	Ringers 3 liters Plasma 2 units Whole blood 7 units	Placed on respirator. G suit left on 24 hrs. then taken off. Transferred to other hosp. 13 days after admission. Now in satisfactory cond.
5	39	Hydroplane driver hit by his boat with resulting open fx & severe soft tissue injur rt humerus, rt femur. Severe lac. posterior thighs bi & open wound rt foot.	85	120/80	Ringers 3 liters Plasma 2 units Whole blood 7 units	Still under care for fractures.
6	78	Pedestrian struck by car with resulting tib-fib fractures, pelvic fx, fractures C 3,4,5, chest trauma	60 systolic	100 systolic	Ringers 4 liters Plasma 4 units Whole blood 7 units	Died 2 hrs 1 min after admission
7	27	Overdose with subsequent resp. arrest and acute abdomen	0	120 systolic	D_5W	Discharged
8	21	Gunshot wound to rt buttock with retroperitoneal hematoma and perforated cecum	Unobtainable	100	Ringers 2 liters D_5W 1.5 liters Whole blood 3 units	Discharged 15 days after admission
9	21	Stab wound to neck with laceration lt common carotid artery	32	104	Ringers 2 liters ... Plasma 3 units Whole blood 6 units	Died 15 days postop secondary to intracerebral thrombus formation

both in urban and rural areas in managing trauma at the scene. We further believe that it should soon be established as standard equipment for ambulances. All ambulance personnel and physicians dealing with emergencies should know of its availability and use.

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Request for Physician's Art Work

For many years the Board of Editors of MINNESOTA MEDICINE has recognized and supported photographic and other artistic talents of the members of the Minnesota State Medical Association publishing cover pictures in color of their work. Our series of color covers have received much favorable comment and many journals have followed us in the use of color art in this manner.

We solicit color photographs including pictures of all art forms created by members of the association. These must be technically excellent to show off the subject to its best advantage.

Although in the past we have printed cover pictures depicting many distant parts of the world, photographs of life in Minnesota will be given preference. Pictures will be returned if identified with the name and address of the physician. Please submit your picture as prospective cover subjects to the Editor of MINNESOTA MEDICINE, 375 Jackson St., St. Paul, Minnesota 55101.

During 1976 the Editors would like to pay homage to the Bicentennial by having our covers depict places, events, objects, scenes, etc., that have historical or patriotic significance for the State of Minnesota. Please keep the Bicentennial theme in mind when submitting prospective covers for 1976.

Farrell Stiegler, M.D.
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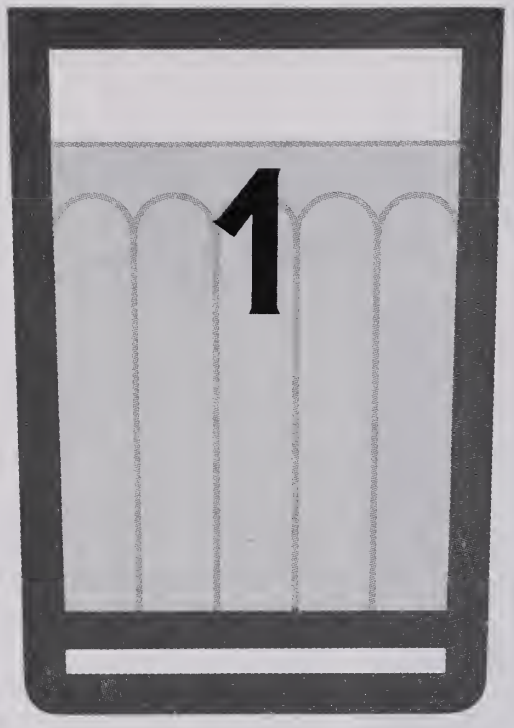
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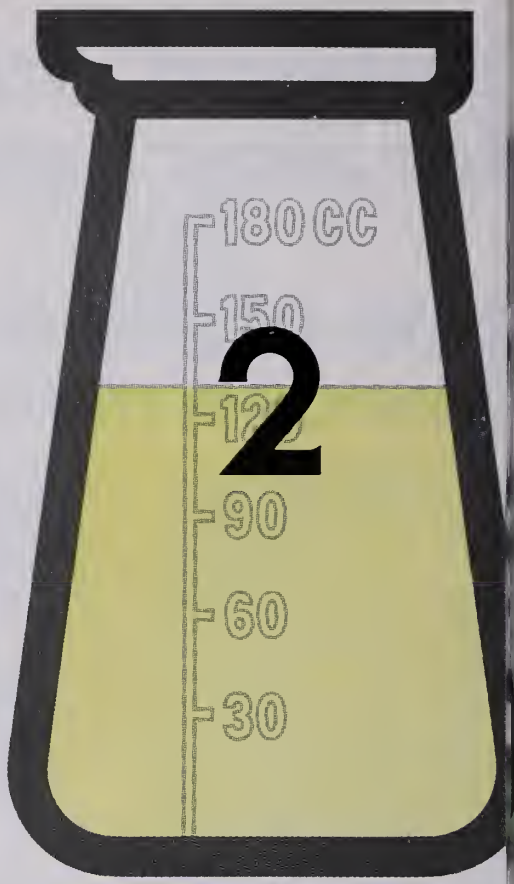
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Warnings: Safety during pregnancy has not been established. Sulfonamides should not be used for group A beta-hemolytic streptococcal infections and will not eradicate or prevent sequelae (rheumatic fever, glomerulonephritis) of such infections. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported and early clinical signs (sore throat, fever, pallor, purpura or jaundice) may indicate serious blood disorders. Frequent CBC and urinalysis with microscopic examination are recommended during sulfonamide therapy. Insufficient data on children under six with chronic renal disease.

Precautions: Use cautiously in patients with impaired renal or hepatic function, severe allergy, bronchial asthma; in glucose-6-phosphate dehydrogenase-deficient individuals in whom dose-related hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias* (agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia); *allergic reactions* (erythema multiforme, skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis); *gastrointestinal reactions* (nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis); *CNS reactions* (headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia); *miscellaneous reactions* (drug fever, chills, toxic nephrosis with oliguria and anuria, periarteritis nodosa and L.E. phenomenon). Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide, thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia as well as thyroid malignancies in rats following long-term administration. Cross-sensitivity with these agents may exist.

Dosage: Systemic sulfonamides are contraindicated in infants under 2 months of age (except adjunctively with pyrimethamine in congenital toxoplasmosis).

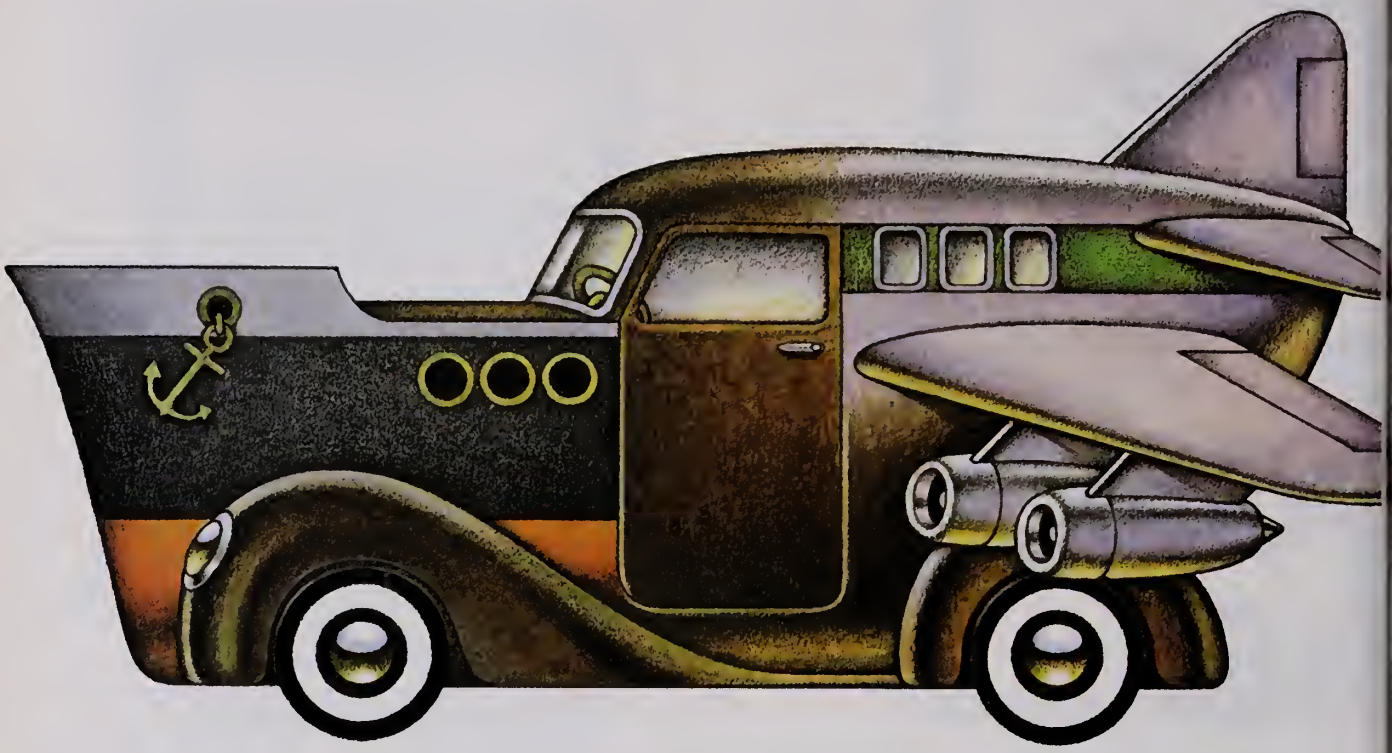
Usual adult dosage: 2 Gm (4 tabs or teasp.) initially, then 1 Gm *b.i.d.* or *t.i.d.* depending on severity of infection.

Usual child's dosage: 0.5 Gm (1 tab or teasp.)/20 lbs of body weight initially, then 0.25 Gm/20 lbs *b.i.d.* Maximum dose should not exceed 75 mg/kg/24 hrs.

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Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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Editorials

Progress in Trauma

TRAUMA IS THE third cause of deaths in the United States. Unlike cardiovascular disease and cancer, which are, respectively, number one and two as leading causes of death, trauma can be controlled to some degree. Motor vehicle accidents now constitute over half of all accidental deaths in America. From 1960 through 1975 deaths from motor vehicle injuries has almost doubled. Speed has been a significant factor. Shortly after the national reduction in highway speed limits to 55 miles per hour all areas of the nation experienced a significant reduction in serious injuries resulting from motor vehicle accidents on the highways. If we consider highway trauma a public health measure, this experience represents one of the clearest examples of large scale benefit to masses of population by a remedial health measure in modern times, along with the conquest of poliomyelitis.

Nonfatal injuries in the United States are now ten times more common than accidents causing death. The cost, in patient morbidity and dollars lost to the economy, is exorbitant. In excess of six billion dollars per year are lost in wages alone following nonfatal accidental injuries, and insurance payments also exceed six to seven billion dollars annually. Trauma is, indeed, one of our most serious health problems.

During the past decade strong interest in trauma has brought improvements in many aspects of management of the trauma victim. First aid methods have been improved with better equipment for resuscitation and transport; large numbers of laymen are now trained more adequately in first aid; ambulance personnel repeatedly receive refresher "trauma courses" in most states of the union; and more rapid and careful transport of the trauma victim is practiced in most parts of the country. Many states are highly organized with designated regional trauma centers located at strategic sites, and capable of providing services of all types of specialists for differing kinds of trauma.

The serious disturbances in pulmonary and renal physiology that result from trauma are now better understood and improved corrective and preventative measures are saving more lives.

With our increasing population and continually increasing mechanization of American society, it is still possible to foresee a future where the incidence of serious sequelae and deaths from trauma can be reduced in relative incidence. This symposium is one evidence of the high quality of the postgraduate educational offerings to be found in many parts of the United States. Considering the welfare of our people in terms of their health, and the overall impact on our economy, we are justified in strongly encouraging greater emphasis in this most important field of medicine and surgery.

Claude R. Hitchcock, M.D., Ph.D.
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The Multiple Trauma Patient

A CRITICALLY INJURED patient is one who has sustained a life endangering injury or a patient with multiple injuries which often result in considerable permanent disability. The injuries of a multiple trauma patient consist of two or more of the following systems: (1) head and neck, (2) chest, (3) abdomen, (4) pelvis, and (5) extremities with the exception of multiple fractures which alone qualifies a patient as a multiple trauma patient.

The records from the United States Department of Highways revealed deaths of 47,000 in 1969, 55,800 in 1973, and 46,200 in 1974. The decreased mortality in 1974 may be attributed to the following: (1) more rapid and careful transport of patients, (2) marked improvement in the overall management of trauma patients, particularly combating shock and better understanding of pulmonary and renal physiology, and (3) reduction in the speed limit to 55 miles per hour.

A multiple trauma patient requires a multiple disciplinary approach. However, it is *mandatory* to have one *primary physician,* preferably a general surgeon, because of the nature of his training, who must be in charge of the team of personnel working with the patient. As soon as the patient is admitted to the surgical intensive care unit, he must be the sole coordinator, giving orders to nurses, writing orders in the chart, and making daily progress notes on the patient's condition. Multiple orders from various specialists confuse the nurses and often times contradict each other. Consultants' notes must be closely identified in the progress notes.

The common errors made during the course of treatment of a multiple trauma patient are: (1) failure to maintain a good airway in an unconscious patient, (2) failure to recognize that unconsciousness is not necessarily the result of an obvious head injury, (3) failure to recognize that co-existent disease may be the cause of the accident or the effect of injury, (4) failure to look for latent injuries, (5) failure to start immediate treatment which can lead to severe, prolonged and crippling complications, (6) failure to recognize the amount of blood loss in apparently unremarkable injuries, and (7) failure to obtain adequate cervical spine Xrays on a comatose multiple injured patient or one with head injuries.

The multiple trauma patient will die from life threatening problems in order of their priorities: (1) airways, (2) shock from blood loss, (3) head and cervical injuries, (4) intraabdominal injuries, and (5) pelvic fractures with intrapelvic injuries.

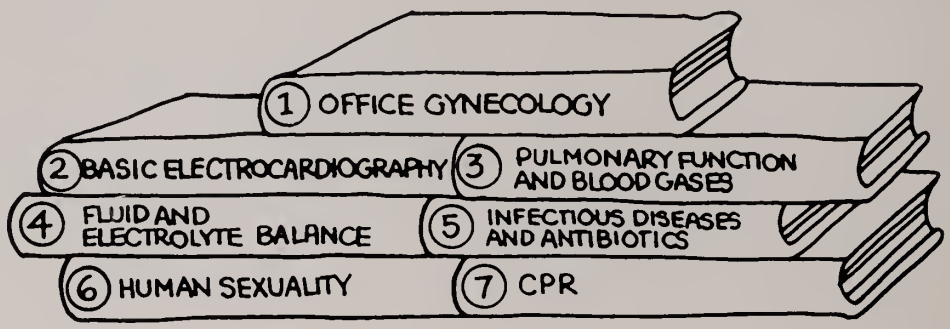
The management of a multiple trauma patient begins at the site of the accident where an experienced ambulance team initiates emergency resuscitative measures such as an application of a G-suit to control shock and massive hemorrhage, splinting of fractures, and administration of intravenous fluids.

The patient is then brought immediately to an Emergency Room staffed by competent and well-trained Emergency Room Personnel consisting of doctors, nurses, and paramedical people. Initial resuscitative measures and establishment of an airway belong to the Emergency Room Physician with help sometimes from either a general surgeon or an anesthesiologist. Rapid assessment and evaluation of the injuries should be made so that listing of problems in order of their priorities can be recorded and treatment initiated. The institution must provide specialists in various fields who can respond immediately within minutes for consultation and treatment, and not one half hour to an hour later. Priorities are immediately decided in a five-10 minute period. Accurate, rapid evaluation, and good initial treatment of a multiple trauma patient determines his immediate and long term prospects for life and disability. Much has been done, but much more has to be done in order to decrease the morbidity and mortality of a multiple trauma patient.

Ramon B. Gustilo, M.D.*
Guest Editor

*Head, Department of Orthopedics, Hennepin County Medical Center, Minneapolis, and Orthopedic surgeon, Metropolitan Medical Center, Minneapolis, Minnesota.

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*Courses 1 through 5 are 6 hours each; each is presented twice (once on Saturday, once on Sunday); and each costs $70. Courses 6 and 7 are 12-hour courses that run both days and their costs depend on package options elected by registrants.

For more information, **WRITE:**
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Letter to the Editor

Dear Editors:

I thought you'd be interested in developments on two issues affecting the private practice of medicine that are currently under consideration in some state legislatures: malpractice claims and comprehensive health insurance.

In his recent State of the State address, Otis R. Bowen, M.D., Governor of Indiana, urged Indiana Legislators to ". . . arrive at a solution . . . a sound and workable solution (to medical malpractice claims). For unless a solution is found, serious harm can occur insofar as Indiana's health care delivery system is concerned."

In addition, Indiana State Representative, Chester F. Dobis, introduced House Bill 1460 which, if enacted, would "provide for the establishment of a Patients' Compensation Board of Indiana to hear and determine claims for damages which are based on an assertion of medical malpractice; to provide for a schedule of compensation; to provide for a guarantee of financial responsibility for health care providers; and to provide that costs of administration be funded by fixed assessments collected from certain health care providers." If you would like additional information on H. B. 1460, you may wish to contact Mr. Dobis at the State Capitol in Indianapolis, Indiana 46204.

Another malpractice item: The American Group Practice Association's Executive Director, James B. Cobb, and Representative James F. Hastings (R-N.Y.) jointly announced a National Conference on Malpractice Insurance, March 20-21.

Concerning National Health Insurance: An alternative to a federal government comprehensive health insurance program has been developed in conjunction with the Conference of Insurance Legislators (COIL)—a group composed of the Chairmen of all State Insurance Committees and the State Insurance Commissioners —with the thought that it would be introduced in all 50 states.

The COIL model bill because, unlike bills for federal NHI programs, it has received very little press coverage. I have not analyzed the bill, have no position on it.

Senator Daniel Foley introduced the COIL Bill in Massachusetts. It would make comprehensive health insurance available to all citizens of the state. In discussing the bill, Senator Foley mentioned that his bill calls for:

—state standards for minimum ambulatory, preventive and institutional care benefits, including comprehensive coverage for catastrophic illness
—phasing in of benefits on a timetable basis for constant upgrading of benefits
—use of existing private health insurers to provide benefits
—establishment of a pool of private health insurers to provide standard benefits for the poor, near-poor and those previously uninsurable for health reasons.

In addition to Massachusetts, the COIL Bill—or some version of it—is being considered in approximately 24 states. These include: California, Connecticut, Hawaii, Kansas, Maine, Michigan, Minnesota, Nebraska, New Mexico, Ohio, Oklahoma, Rhode Island, Vermont, Washington and Wisconsin. If you have any comments or questions, you may wish to contact Senator Foley at the State House in Boston or the Chairmen of the Insurance Committees in your state.

Edward F. X. Lawlor, Jr.
Manager
National Health Affairs
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L'Hôtel-Dieu de Québec



Seventeenth-century Hôtel-Dieu de Québec, model on display in the hospital's museum.

The first hospital in Canada was organized and financed by Cardinal Richelieu and his niece, the Duchess d'Aiguillon. In 1637 they signed a contract with the Augustinian sisters of the hospital at Dieppe, and by 1639 three nuns, all under age thirty, had opened the new hospital in a six-room log house at Quebec. Its first physician was Robert Giffard, Seigneur of Beauport, the only medical man at Quebec at the time and the father of the first Canadian-born girl to join the hospital's nursing order.

After a four-year sojourn at near-by Sillery, a move calculated to bring the sisters closer to the Indians they hoped to serve, the hospital returned to Quebec where new construction completed in 1646 resulted in a proper hospital building resembling the established institutions of France. A part of the building erected in 1695, with stone walls several feet thick and close-set hand-hewn rafters and door casings, is still in use as the sisters' residence.

The Hôtel-Dieu survived the three major sieges of Quebec, among them the one culminating in the battle between the armies of Generals Wolfe and Montcalm on the Plains of Abraham in 1759. In the hospital's museum there is today a collection of cannon balls, all dug up from the hospital garden, relics of the institution's battle-scarred past. Also on display is a wooden chest brought from France by the original three nuns in 1639.

From the beginning the Hôtel-Dieu de Québec has cared for the poor free of charge. In 1757 the hospital was receiving an allowance of six sous (about five cents) per day for the care of soldiers and ten to fifteen sous for merchant seamen. Today all patients are covered by government insurance, but may be charged as much as six dollars per day, if able to pay.

Presently the hospital has 600 beds, is a teaching facility of Laval University, and is still staffed by the Augustinian sisters. It is an active radiation therapy center and also averages about one kidney transplant per week.

Warren L. Kump, M.D.
Minneapolis, Minnesota

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Philosophical Musings

Senior Citizens Half-Price?

Why not? After membership in a lodge, club or his County or State Society, for a specified number of years, absolution from dues should be accorded the Senior Citizen. Fees already paid by him constitute an investment, the interest on which should be sufficient to carry his membership for the rest of his life. Such a prerequisite could pay off handsomely for the organization when the Senior member, taking advantage of his entertainment privileges, would invite guests to join him in suptuous dinners or elaborate entertainment, generously hosting at his own expense, usually at an hour preceding the busy schedule.

Ski resort areas well realize the advertising value of the Senior Citizen's presence and almost universally admit him to the lifts at half-price. A few even welcome him free, for they observe that frequently he will bring along children and grandchildren, gladly paying their expenses—from snacks and drinks to four-course dinners, even to overnight housing.

Besides being practically profitable, the presence of a distinguished oldster gives the place an aura of dignity and prestige, convertible into a more intangible monetary advantage.

Considering that restless, inquisitive, uncoordinated four-year-olds and their teenage counterpart cover much more ground in their mindless scrounging; occupy much more space, monopolizing the most comfortable chairs; make much more noise, assaulting the air with shattering screeches and deafening shouts for attention by demanding a drink of water every few minutes or emergency assistance to the toilet, Senior Citizens should be a relief. They don't tax the patience and exhaust the endurance of other guests or employees in public or private places. They are quiet and sedate, satisfied to find a comfortable chair and remain there for the duration of a stimulating and mutually profitable conversation.

When accompanied by parents, youngsters are allowed in hotels free, where they jump up and down on the beds; waste the bath water and the electricity; ride the elevators, plugging in each floor just for kicks; and run collision courses up and down the halls and stairways. Not so the oldsters! After registering they retire to the silence and privacy of their rooms, content to relax there, perhaps at a window in the dark enjoying the urban panorama below: rhythmic traffic and semaphore signals in a fascinating color kaleidoscope. They don't leave faucets running; drop things into the toilet; write on the walls; scribble on the hotel tablecloth; blare the radio or television; or wet the bed.

We could cite innumerable other instances where Senior Citizens might justifiably be charged less than other age groups or even be free-riders. After all, they have long since qualified, haven't they?

Carl O. Rice, M.D., Ph.D.
Editor Emeritus

Letters to the Editor

We would like to encourage physicians to contribute to the Letters to the Editor Section. We want to hear what you have to say, what you think, why you hold certain opinions. In short, we want to make this as lively and spirited a section as possible.

The Editors

In Appreciation

We are sincerely pleased to acknowledge the firms listed below who participated in the 1975 Annual Meeting Exhibit. The exhibits were attractive and informative. The financial support provided by these exhibitors contributes significantly to meeting the costs of our fine scientific program and related activities. May we urge that you personally acknowledge this support to representatives of these firms as the opportunity to do so may occur. We heartily invite their participation in the 1976 Annual Meeting in Rochester.

G. R. Diessner, M.D.
President

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*These firms have exhibited at 10 or more consecutive Minnesota State Medical Association Annual Meetings.

adjunctive therapy for wound debridement

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HELPS PREPARE WOUND FOR:

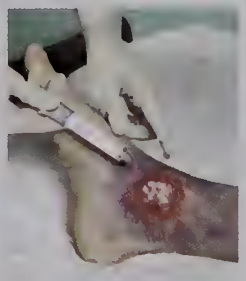
- Granulation/Healing
- Granulation/Grafting



CLEANSE WOUND
Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials.



THOROUGHLY MOISTEN
Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g., sodium chloride or water solutions).



APPLY ENZYME
Apply a layer of TRAVASE Ointment. Assure intimate contact with necrotic tissue and complete wound coverage.

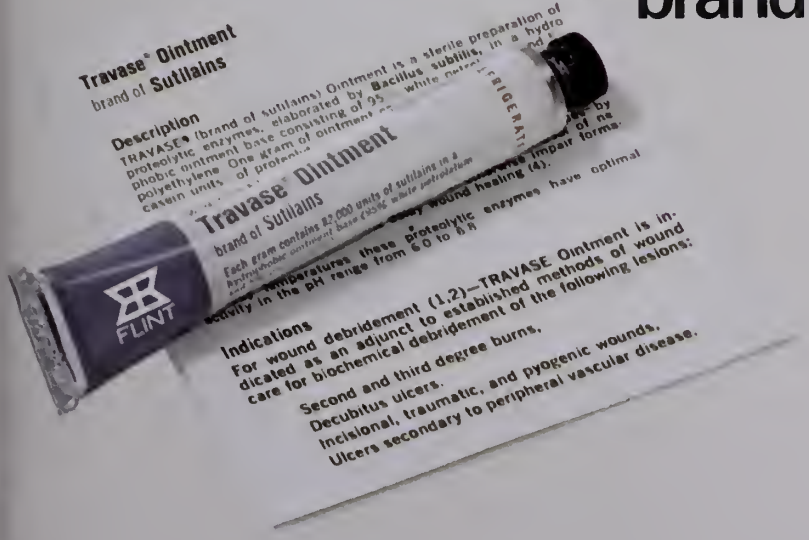


APPLY MOIST DRESSING
Apply loose moist dressings (most important with dry leathery eschar).



CHANGE DRESSINGS
When changing dressing, gently wipe away the dissolved material. Repeat the procedure, including application of TRAVASE Ointment, 3 to 4 times per day for best results.

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Indications
For wound debridement (1,2)—TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:
Second and third degree burns,
Decubitus ulcers,
Incisional, traumatic, and pyogenic wounds,
Ulcers secondary to peripheral vascular disease.

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Travase® Ointment brand of Sutilains

ulcers

TERRY V. CARLE, M.D., CLINICAL INSTRUCTOR, DEPT. OF PHYS. MED. & REHAB., CRAIG REHABILITATION HOSPITAL, UNIVERSITY OF COLORADO



Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



After nine days of TRAVASE therapy, debridement is nearly complete and granulation evident.

burns

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Before treatment . . .



48 hours following treatment with TRAVASE Ointment on right hand; left hand is control.

Travase® Ointment

(brand of Sutilains)

Indications: For wound debridement, TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

- Second and third degree burns,
- Decubitus ulcers,
- Incisional, traumatic, and pyogenic wounds,
- Ulcers secondary to peripheral vascular disease.

Contraindications: Application of TRAVASE Ointment is contraindicated in the following conditions:

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- Wounds containing exposed major nerves or nervous tissue,
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Adverse Reactions: Consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

DOSAGE AND ADMINISTRATION: STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECTIVE RESULTS OF TREATMENT:

1. Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., hexachlorophene, silver nitrate, benzalkonium chloride, nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g. sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

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Special Article

Gunshot Wounds to the Extremities

Early Treatment

RAYMOND L. STRUCK, M.D.* and RAMON B. GUSTILO, M.D.†

A review of seventy gunshot wounds to the extremities treated at Hennepin County Medical Center and a review of the literature on the subject is given. For treatment purposes, these wounds are divided into high velocity, low velocity, and shotgun wounds as differences in the pathophysiology of each may lead to errors in treatment.

To place all gunshot wounds into one category oversimplifies a complex subject. It may lead to improper assessment and consequently improper management. The intent of this paper is to assess our 1972 to 1974 experiences with gunshot injuries at Hennepin County Medical Center and to discuss various aspects of these injuries.

Most authors separate gunshot injuries into high velocity and low velocity wounds. They also put shotgun wounds into a different category. Therefore, the wounds in this study are divided into three groups (Table 1).

TABLE 1
Classification

Type	Muzzle Velocity (ft/sec)
Low Velocity	0-1800
High Velocity	1800-3250
Shotgun	1100-1350

Materials and Methods

Seventy-seven patients with ninety-one extremity gunshot wounds were admitted to the orthopedic or general surgery services at Hennepin County Medical Center between April 1, 1972 and April 1, 1974. About ten per cent of all gunshot wounds seen in the Emergency Room at this institution were directly treated and released because of superficial wounds. They were not included in this study. Admitted patients had significant soft tissue damage, a penetrating wound, an associated fracture, or a question of neurovascular damage.

Because of inadequate followup, eighteen patients with twenty-one wounds were excluded from the study. Followup was judged adequate if the patient was seen a minimum of ten days after injury and if the hospital chart showed healing had occurred. Followup in fifty-nine patients with seventy wounds comprise this study (Table 2). The type of low velocity firearm used was identified in thirty-eight wounds and was unknown in twenty-four. The wounds were classified depending upon whether they were perforating or penetrating and whether or not the projectile was removed. Forty-one were perforating and twenty-nine were penetrating. Of the twenty-four penetrating low velocity wounds, fourteen bullets were removed, five remained, and what happened to the other five was not mentioned. Thirty-two injuries involved the upper extremities, and thirty-eight the lower extremities and hip. Twenty-four fractures were associated with the sixty-two low velocity wounds. Both high velocity wounds had associated fractures. This distribution of fractures followed the distribution of the wounds.

TABLE 2
Gunshot Wounds Encountered

Low Velocity	62
High Velocity	2
Shotgun	6 (4 close range)
TOTAL	70

Treatment

Basic treatment of all wounds consists of copious irrigation of the wound and the debridement of skin edges. High velocity wounds and close-

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*Orthopedic Resident, Hennepin County Medical Center, Minneapolis, Minnesota.

†Head, Department of Orthopedics, Hennepin County Medical Center, Minneapolis, Minnesota.

Orthopedic Surgeon, Metropolitan Medical Center.

range shotgun wounds receive more extensive debridement of the wound tract. Thirty-eight of the seventy wounds were treated in the operating room including thirty-two of the sixty-two low velocity wounds, both high velocity wounds and all four close range shotgun wounds (Table 3).

TABLE 3
Basic Treatment of Gunshot Wounds

Copious Irrigation
Debridement of Wound Tract and Skin Edges
Tetanus Toxoid
Antibiotics
Delayed Closure

Wound Closure

Table 4 summarizes the types of wound closure. Of the sixty-two low velocity wounds, ten were closed primarily, sixteen had delayed primary closure, thirty-five achieved healing by secondary intention, and one required a split thickness skin graft. One high velocity wound was closed by delayed primary closure and one required skin grafting. Two shotgun wounds were closed by delayed primary closure, three healed by secondary intention and one required multiple skin grafts. In all wounds complete healing were obtained.

TABLE 4
Wound Closures

Type	Primary	Delayed Primary Closure	Secondary Intention	Skin Graft
Low Velocity	10	16	35	1
High Velocity		1		1
Shotgun		2	3	1
TOTAL	10	19	38	3

Antibiotics

All but two patients received intravenous antibiotics consisting of either Cephalothin or a combination of Oxacillin and Ampicillin for about three days after injury. These forms of antibiotic therapy are chosen because they cover both gram negative and gram positive organisms. Routinely, 0.5 cc's Tetanus Toxoid I.M. is also administered to each patient.

Cultures

Cultures were obtained prior to irrigation in twenty-three wounds, immediately after irrigation in twenty-one wounds, and in eleven wounds at a later date either at the time of delayed primary closure or because of a suspected wound infection. Fifteen of the twenty-three cultures obtained prior to irrigation grew various gram negative and gram positive bacteria indicating most wounds are contaminated.

Three of twenty-one cultures taken after irrigation grew bacteria, and positive cultures have been obtained at later dates in five of eleven wounds.

Infections

Infection was considered if any of the following existed: erythema, induration, wound drainage, and a positive culture. Two infections are documented this way in sixty-two low velocity wounds for an incidence of 3.2 percent. One was infected with staphylococcus coagulase positive and the other was a pseudomonas infection in a shoulder wound that required a saphenous vein graft for repair of the axillary artery. This wound was closed primarily. Local wound care and antibiotics controlled both infections. Neither high velocity wound manifested evidence of infection. One shotgun wound with persistent drainage grew coagulase negative staphylococcus on numerous cultures. Healing subsequently occurred without further evidence of infection.

Complications

Late complications of low velocity wounds include an atraumatic knee effusion six months after arthrotomy and bullet removal, a nonunion of a metatarsal fracture, and traumatic arthritis of a hip that necessitated removal of a bullet from the cartilaginous cap of the femoral head three months after injury. High velocity wound late complications include decreased function and range of motion in a hand secondary to tendon and nerve damage, and nonunion of a femoral fracture requiring an ASIF blade plate and bone grafting. Sympathetic neuritis of both legs requiring lumbar sympathetic blocks and an open refracture at the wound site with subsequent development of a pseudomonas osteomyelitis in a tibial fracture were late sequelae of the shotgun wounds in this series.

Discussion

Low velocity wounds comprise most civilian gunshot injuries,[10,11,12] but enough high velocity wounds and shotgun injuries occur for hunting accidents and domestic quarrels to make it imperative for surgeons to know how to treat and evalu-

ate different types of wounds.

There are three basic aspects of wounding capability. The first is the amount of kinetic energy imparted by the projectile to the target of impact. The second is the type of bullet or projectile dispensed from the firearm. The third is the biochemical characteristics of the tissue absorbing the energy.

Kinetic Energy

The kinetic energy imparted to the target depends on the bullet mass, the second power of the muzzle velocity of the particular firearm as expressed in the equation K.E. = $\frac{1}{2}MV^2$, and the distance to the target. Table 5 gives examples of various firearms and their muzzle velocities. All "Saturday Night Specials" and other hand guns fall into the low velocity range, while military rifles or big game hunting rifles are high velocity firearms.

TABLE 5
Muzzle Velocities of Common Firearms

Weapon	Muzzle Velocity (ft/sec)
.22	1012
.32	964
.38	1146
.357 Magnum	1430
Shotgun	1100-1300
30.06	2700
M16	3250

The amount of tissue damage in a wound is also partly dependent on the specific gravity and elasticity of the type of tissue involved. Animal experiments reveal that tissues such as lung and fat with low specific gravities and high elastic content are more resilient and show less tissue destruction.[6] Liver, muscle and skin are intermediate, while bone tends to show greater destruction.

Low velocity wounds characteristically leave a small wound tract with a minimal amount of tissue destruction. They are readily treated with irrigation and ellipsing of the wound edges providing no fracture or major vascular injury is present. At this institution all but two were treated with IV antibiotics with an infection rate of 3.2 per cent. Infection was not found in any of our wounds which had projectile fragments remaining. If the bullet is easily accessible or the patient experiences pain or discomfort it should probably be removed.[11] We feel a major operative procedure is not indicated for removal of a bullet unless it gives significant symptoms or there is a possibility of damage to a major structure by migration of the fragments. Delayed primary closure is recommended for these wounds.

Every high velocity missile wound must be considered from two points of view; the permanent wound tract or the obvious tissue damage caused by the bullet, and the temporary wound cavity. This temporary wound tract or "cavitation injury" forms a fraction of a second after impact during passage of the missile through the target. This tract results from the large amount of kinetic energy absorbed by the target and occurs only with high velocity injuries. The high velocity missile acts as an explosive force and causes surrounding cells to act as secondary missiles thereby massively increasing the amount of tissue damage. Pressures up to one hundred atmospheres have been measured in the cavity immediately after impact,[3] accompanied by tissue recoil and a negative sucking force causing various types of debris to be included in the wound tract. Copious irrigation and wide debridement are recommended for those wounds along with intravenous antibiotics. Not infrequently these wounds have associated unstable fractures and neurovascular injuries. The fractures should generally be treated conservatively without internal fixation because of the danger of infection. One indication for internal fixation of a fracture may be associated major arterial or nerve injury necessitating repair and absolute immobility for healing.[14] Delayed closure is indicated for these wounds also.

High velocity missiles have been demonstrated experimentally and clinically to have the capacity to cause fractures and major vascular injury at some distance from the obvious wound tract due to the cavitation effect. All nonviable tissue must be excised. If a question arises and the tissue can be spared, it is best to excise it. Wound tracts near major vascular structures should be explored to ensure patency of the vessel involved. If the repair of a major vessel is to be undertaken it is best to use a synthetic or venous graft and adequately debride the injured vessel walls.[14]

Shotgun injuries are considered separately for several reasons. They tend to cause massive soft tissue damage at close range because of the muzzle energy generated. Sherman and Parrish found in their analysis that the mortality from shotgun

wounds was more than twice that of other gunshot wounds in civilian practice.[16] At close range these wounds behave like high velocity wounds, whereas at long range they produce a low velocity type of wound. At close range very little scatter of the charge occurs and the missile striking the target includes not only the shot charge but the wadding as well, which is known to be of a noxious nature. The wadding is an organic material usually made of cattle hair and jute with fragments of woven burlap in each wad. Paradies and Gregory have indicated that penetrating shotgun wounds particularly have a greater tendency to contain this material which greatly enhances the danger of deep wound infection.[13] It is their observation that the wadding travels for a distance of up to thirty yards before striking the ground at skeet ranges and therefore any close-ranged blast may contain this material.

Generally, it can be assumed that the smaller the entrance wound from a shotgun injury the greater will be the amount of tissue destruction because a small entrance wound indicates a close range injury. Copious irrigation and extensive debridement is necessary with these wounds. Primary closure and even delayed primary closure are probably not indicated and the safest approach with a close range injury is probably packing open and split thickness skin grafting over a good granulating bed of tissue. Major vascular and nerve damage is also more common with close range shotgun injuries and needs to be recognized and explored immediately. Antibiotics are indicated with these wounds because of the possible presence of wadding and other debris contained within the wound. Long range shotgun injuries with only a few pellet holes may be treated with the usual modalities used in low velocity wounds.

Conclusion

Results of a two year retrospective study on gunshot wounds to the extremities treated at Hennepin County General Hospital and a review of the literature dealing with this problem are given. Our conclusions and recommendations are the following:

1. Most civilian gunshot wounds are low velocity in nature.
2. Basic treatment of all gunshot wounds consists of adequate debridement, copious irrigation and administration of Tetanus Toxoid. Delayed closure is recommended in all wounds.
3. Results of cultures taken in our series show that gunshot wounds may be contaminated with an assortment of gram positive and gram negative bacteria and therefore broad spectrum antibiotic therapy should be used when indicated.
4. Differences in the pathophysiology of the three types of wounds encountered must be kept in mind. The physician treating these injuries should be aware of the cavitation effect of high velocity and close range shotgun injuries so that adequate debridement and exploration for associated neurovascular injuries are accomplished. A thorough search for wadding and other foreign debris must also be made in these wounds.
5. A three-day course of broad spectrum antibiotic therapy is recommended for high velocity injuries, close-range shotgun wounds, and low velocity wounds with associated open fractures. The efficacy of antibiotic therapy in other low velocity wounds remains controversial.

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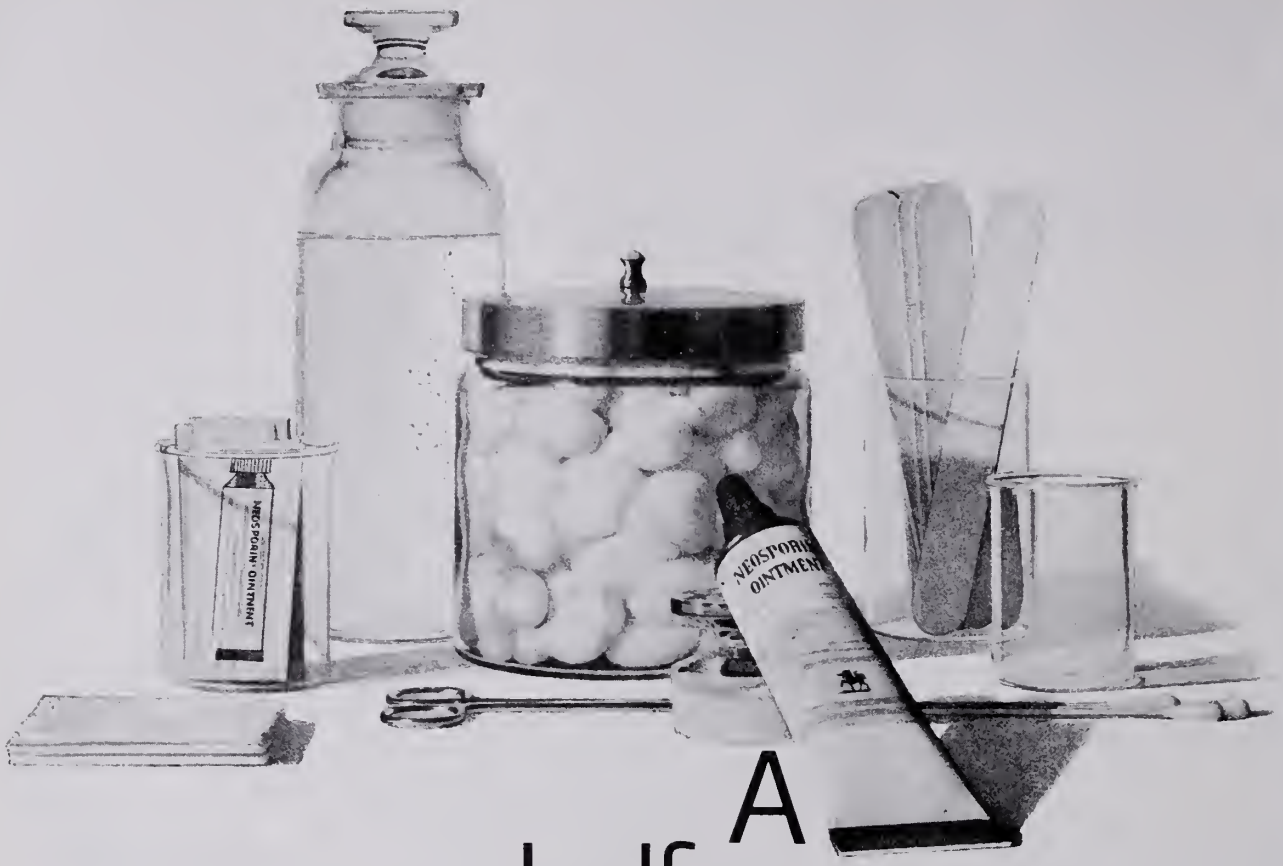
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Use it to prevent a topical infection. Or to treat one that's already started. In either case, it's good medicine. Whether for lacerations, burns, open wounds, IV catheter or surgical aftercare. Neosporin® Ointment provides broad antibacterial coverage against common susceptible pathogens. And since it contains three antibiotics that are rarely used systemically, the risk of sensitization is reduced. Neosporin Ointment. A half-ounce of prevention. Also available in a full ounce of prevention and in convenient foil packets.

Neosporin Ointment carried on Apollo and Skylab missions.

Neosporin® Ointment
(polymyxin B-bacitracin-neomycin)

Each gram contains: Aerosporin® brand Polymyxin B Sulfate 5,000 units; zinc bacitracin 400 units; neomycin sulfate 5 mg (equivalent to 3.5 mg neomycin base); special white petrolatum qs.
In tubes of 1 oz and 1/2 oz and 1/32 oz (approx.) foil packets.

INDICATIONS: *Therapeutically,* used as an adjunct to appropriate systemic therapy for topical infections, primary or secondary, due to susceptible organisms, as in: • infected burns, skin grafts, surgical incisions, otitis externa • primary pyodermas (impetigo, ecthyma, sycosis vulgaris, paronychia) • secondarily infected dermatoses (eczema, herpes, and seborrheic dermatitis) • traumatic lesions, inflamed or suppurating as a result of bacterial infection.
Prophylactically, the ointment may be used to prevent bacterial contamination in burns, skin grafts, incisions, and other clean lesions. For abrasions, minor cuts and wounds accidentally incurred, its use may prevent the development of infection and permit wound healing.

CONTRAINDICATIONS: Not for use in the eyes or external ear canal if the eardrum is perforated. This product is contraindicated in those individuals who have shown hypersensitivity to any of the components.

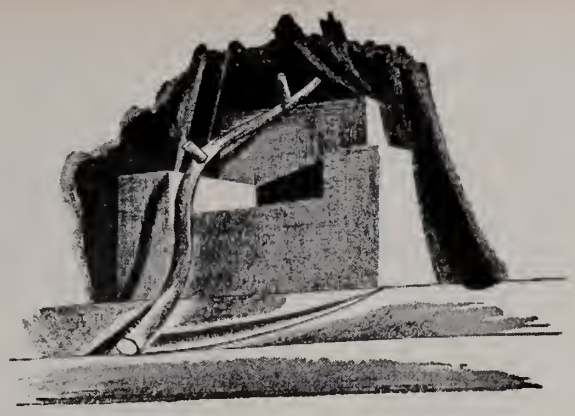
WARNING: Because of the potential hazard of nephrotoxicity and ototoxicity due to neomycin, care should be exercised when using this product in treating extensive burns, trophic ulceration and other extensive conditions where absorption of neomycin is possible. In burns where more than 20 percent of the body surface is affected, especially if the patient has impaired renal function or is receiving other aminoglycoside antibiotics concurrently, not more than one application a day is recommended.

PRECAUTIONS: As with other antibacterial preparations, prolonged use may result in overgrowth of nonsusceptible organisms, including fungi. Appropriate measures should be taken if this occurs.

ADVERSE REACTIONS: Neomycin is a not uncommon cutaneous sensitizer. Articles in the current literature indicate an increase in the prevalence of persons allergic to neomycin. Ototoxicity and nephrotoxicity have been reported (see Warning section).

Complete literature available on request from Professional Services Dept. PML.

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Research Triangle Park
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In Memoriam

WILBERT WM. YAEGER, M.D.

Dr. Wilbert W. Yaeger, former Marshall physician, died January 26th in Laguna Hills, California. Dr. Yaeger was active in the organization of Minnesota Blue Shield and served on its board of directors from its beginning until 1960.

He was a graduate of the University of Minnesota Medical School, a member of the Lyon-Lincoln County Medical Society and the American Medical Association, and an Associate Member of the Minnesota State Medical Association.

Dr. Yaeger is survived by his wife, Adele, and two daughters, Joanne and Jackie.

LLOYD A. WHITESELL, M.D.

Dr. Lloyd Ashley Whitesell, 67, died December 8th. He was a surgeon and had obtained his medical education from the University of Minnesota Medical School.

Dr. Whitesell was a member of the Hennepin County Medical Society and the American Medical Association and an Associate Member of the Minnesota State Medical Association.

He is survived by his wife, Charlotte, sons, Dr. Lloyd Whitesell, Jr. of Buffalo, and Albert, and daughter, Jean.

CHAS. L. STEINBERG, M.D.

Dr. Chas L. Steinberg, St. Paul pediatrician, died January 31. His medical education had been obtained at the University of Colorado.

He was a member of the Ramsey County Medical Society, the American Medical Association and the Minnesota State Medical Association. Dr. Steinberg was also a diplomate of the Board of American Pediatrics.

HERMAN J. JUST, M.D.

Dr. Herman J. Just, Hastings physician, died May 11. He was 75 years old. In 1943 he opened his practice in Hastings and maintained it until his death. He was the first Staff President of the Regina Memorial Hospital and also the first president of the Mississippi Valley Clinic and one of the four physicians who established it.

Dr. Just was a member of the American Academy of Family Physicians, the American Medical Association, Wakota County Medical Society and a Life Member of the Minnesota State Medical Association. He was to be honored into the 50 Club at the Association's Annual Meeting last May.

Dr. Just is survived by his wife, Rose, and two daughters, Sharon and Diane.

MARKHAM J. ANDERSON, M.D.

Dr. Markham J. Anderson, 79, retired consultant in medicine at the Mayo Clinic and instructor in medicine for the Mayo Foundation Graduate School of Medicine, died March 10, in Sun City, Arizona.

He was born in Rochester and earned his doctor of medicine degree from the University of Minnesota. His appointment to the Mayo Clinic staff was in 1929.

Dr. Anderson was a member of the American Medical Association, Zumbro Valley Medical Society and was an Associate and 50 Club Member of the Minnesota State Medical Association.

He is survived by his wife, Alice, three daughters, Martha Jane, Mary Alice and Charlotte, and a son, Dr. Markham J. Anderson, Jr. of the Mayo Clinic.

HYMAN J. WOLKOFF, M.D.

Dr. Hyman J. Wolkoff, St. Paul physician, died November 17. He was 68. His medical education had been obtained at the University of Minnesota.

Dr. Wolkoff was a member of the Ramsey County Medical Society, the American Medical Association and the Minnesota State Medical Association.

A. ELLIOTT VIK, M.D.

Dr. A. Elliott Vik, Minneapolis surgeon, died November 16. He was 80 years of age.

Dr. Vik was a member of the Hennepin County Medical Society and the American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

He is survived by his wife, Ruth.

ORIANNA McDANIEL, M.D.

Dr. Orianna McDaniel, a pioneer woman physician, died March 12 at the age of 102. Born in Durham, New Hampshire, Dr. McDaniel received her medical education at the University of Michigan in 1894.

She joined the Minnesota State Health Department in 1896 as the first woman physician on its staff. She was with the department about 50 years and was head of the Division of Preventable Diseases from 1921 until her retirement in 1946 at the age of 74.

She was a member of the Hennepin County Medical Society and the American Medical Association and a 50 Club and Associate Member of the Minnesota State Medical Association.

Dr. McDaniel is survived by several grandnieces and grandnephews.

CARNOT H. SHERMAN, M.D.

Dr. C. H. Sherman, Bayport surgeon, died February 26th. He had practiced medicine in Bayport and other areas for over 50 years. He was born near Mount Vernon, South Dakota, and attended medical school at Northwestern University.

He was a member of the Wakota Medical Society and the American Medical Association and a 50 Club and Life Member of the Minnesota State Medical Association.

His wife, Hila, and daughter, Phyllis survive him.

IRVIN H. MOORE, M.D.

Dr. Irvin H. Moore, Minneapolis pediatrician, died March 15. He was 68 years old. Born in Mahaska County, Iowa, Dr. Moore obtained his medical degree at the University of Iowa.

He was a member of the American Medical Association and the Hennepin County Medical Society and an Associate Member of the Minnesota State Medical Association.

Dr. Moore is survived by his wife, Eileen.

S. C. SCHMITT, M.D.

Dr. S. C. Schmitt, retired physician formerly practicing in Los Angeles, died May 26. He was 102 years old. His medical education was obtained at Rush Medical College, University of Chicago, and the University of Minnesota Medical School.

Dr. Schmitt was a member of Hennepin County Medical Society and the American Medical Association and a 50 Club and Associate Member of the Minnesota State Medical Association.

JOSEPH PAUL SPANO, M.D.

Dr. Joseph P. Spano, 69, Minneapolis physician and surgeon, died April 15. He was a former chief of surgery at St. Barnabas Hospital, a graduate of the University of Minnesota and a member of the Elliot Park Clinic.

Dr. Spano was a member of many state and national medical groups. He is survived by his wife, Margaret, and two sons, Joseph Jr. and Wyman L.

ERNEST R. ANDERSON, M.D.

Dr. Ernest R. Anderson, 75, Minneapolis surgeon, died January 15. His medical education was obtained at the University of Chicago Medical School.

Dr. Anderson was a member of the Hennepin County Medical Society, American Medical Association, Minneapolis Academy of Medicine, Minnesota Surgical Society, Great Northern Railway Surgeons Association, and an Associate Member of the Minnesota State Medical Association. He was a former secretary and president of the Minneapolis Academy of Medicine, a former recorder, secretary and president of the Minneapolis Surgical Society and a former second vice president of the Hennepin County Medical Society. He was to be honored as a 50 Club Member at the May meeting of the Minnesota State Medical Association.

He is survived by his wife, Dagmar, and daughter, Judy.

RAE T. LAVAKE, M.D.

Dr. LaVake was born in New York City in 1883 and graduated from the Columbia University School of Physicians and Surgeons in 1909. In 1912 he became associated with the University of Minnesota as Assistant Professor in this specialty. He died March 4th at the age of 92.

He was a former secretary-treasurer of the Minnesota Academy of Medicine, a Fellow of the American College of Surgeons, and a member of the Hennepin County Medical Society, American Medical Association, Minnesota Pathological Society, the American Association of Obstetricians and Gynecologists, the American Board of Obstetrics and Gynecology and a 50 Club and Life Member of the Minnesota State Medical Association.

Dr. LaVake is survived by his wife Elizabeth, and son, James.

FRANCIS A. CARMICHAEL, III, M.D.

Dr. Francis A. Carmichael, III, 36, Duluth radiologist, died May 1. He was born in Rochester and was a graduate of the University of Kansas Medical School. He did his internship at Kansas City General Hospital. Since 1971 he was with the St. Luke's Hospital in Duluth in the Radiology Department.

He was a member of the Minnesota State Medical Association, the American Medical Association and the St. Louis County Medical Society.

Dr. Carmichael is survived by his wife, Janice, two sons, Quinn and Patrick.

HENRY E. NELSON, M.D.

Dr. Henry E. Nelson, 96, Crookston's pioneer doctor, died December 4. He was born in a log cabin in Highland Township Iowa. His medical education was obtained at the Medical School of Iowa City and the University of Illinois.

Dr. Nelson played professional baseball with the Three I League, forerunner of the Minnesota Twins, under the guise of "Home Run Hank," to help defray medical school expenses. He was Polk County coroner for nearly half a century, named Eagle of the Year for the Crookston Lodge, received recognition for being a 50 year Mason by the AF and AM 141, Crookston Chapter. In addition, Dr. Nelson was a member of the Red River Valley Medical Society, the American Medical Association, and an Associate and 50 Club Member of the Minnesota State Medical Association.

He is survived by four brothers and one sister.

EDWARD SCHONS, M.D.

Dr. Edward Schons, 90, died March 3. He was a St. Paul radiologist, receiving his medical degree from Hamline University and the Minneapolis College of Physicians and Surgeons.

He was a member of the American Roentgen Ray Society, Radiological Society of North America, American College of Radiology, the Ramsey County Medical Society, American Medical Association, a Fellow of the American College of Physicians and a Life and 50 Club Member of the Minnesota State Medical Association.

Dr. Schons is survived by his son, William.



Book Reviews

FAMILY CARE by Naomi Baumslag, M.D. The Williams & Wilkins Company, Baltimore, Maryland 1973. 392 pages, $7.95.

If there is a contest for the worst book of the year, this one should be a winner. In the foreword, Dr. Lynn R. Carmichael stated that "it is my hope that this handbook will grow and that the students who use it will add to it. The knowledge and skills they acquire will soon exceed that of their instructors, and, perhaps they will produce a textbook of family medicine." I think that the prospective buyer would do well to wait for a later edition.

As a textbook, it suffers from the identity crisis of Family Practice—General Practice. In the first two chapters, Dr. Baumslag discusses "The Family," "Home and Community," and "Some Thoughts on Attitudes and Cultures." The subject matter in these chapters covers the fields of sociology, anthropology, and social psychology. I could not determine from the acknowledgments that a career behavioral scientist had assisted Dr. Baumslag in writing these chapters and professional input in these areas was not apparent from the text itself.

This is a small book (6″ x 9″) with wide margins and wide spaces between lines. The average page appears to contain less than 250 words. For this reason, if a student were to try to use this as a textbook of pediatrics or medicine, this 390 page paperback contains so little detail as to be practically worthless. It is hard to imagine a medical student so unsophisticated that he could benefit from a presentation on such a simplistic level.

The chapter on family dentistry, which fortunately was one of the longest chapters, was written by Allan Drinnan and appeared to be excellent and probably directed toward the first year medical student who is usually deficient in his knowledge of family dental care.

As I painfully worked my way to the back of the book, I discovered that 4 of its 14 chapters were devoted to various aspects of laboratory medicine. I could not understand why this should be a major part of a book entitled "Family Care." A search of the acknowledgments section provided the clue—Dr. Baumslag's husband is a pathologist and was responsible for these sections.

It was this chance discovery that made the whole book take on a new meaning. At first glance, the book appeared to be a textbook on family care written by Naomi Baumslag, M.D. This inference was unescapable as her name appeared in solitary splendor in ¼″ letters on the bright yellow cover. As I counted the pages in the book it appeared that she had collaborated with other authors on a few chapters but was the sole author of only 37 pages. Her husband, whose name appeared in fine print in the acknowledgments section, had written 39 pages. It seems that the womens liberation movement has made a solid advance into the area of writing text-

John O'Leary, M.D.
University of Minnesota

CLINICAL CHILD PSYCHOLOGY, edited by Gertrude Williams, Ph.D., and Sol Gordon, Ph.D., Behavioral Publications, New York, 1974, 545 pp. $19.95.

Clinical child psychology is a paramedical speciality in its youth. Few universities offer specific training in this field. Few books are available on this subject; this is one of the first.

Over 400 authors contribute. The editors depart from usual paths. They present the new controversial rather than the traditional. They divide the book into more sections with a commentary for each section. The sections cover subjects from children's services and child advocacy to developmental child care education. The concept of intellect is dealt with as well as dealing with sexuality of children and family planning.

The topics within each section offer many opinions. Some chapters represent revised editorials and essays from journals and newsletters. The editors have searched for stimulating commentary, rather than set definitions, in this as yet not fully resolved field.

One trend in the book is prominent—search. This is reflected in the entire book, but is seen explicity in the last section. Here several authors weigh traditional forerunners versus emerging concepts of clinical child psychology. The new models point to ecological spheres of action in the mental health of children.

Child psychiatry calls itself an established field recognized as a subspeciality of its parent—psychiatry. Traditionally it has looked to child psychology as a basic science in defining principles of child development via research modes or in testing of children's potential. As clinical child psychologists move into new concepts, it appears that child psychiatry, too, needs to define its future.

Dorothy M. Bernstein, M.D.
Minneapolis, Minnesota

BEDSIDE DIAGNOSIS. by Charles Seward. 582 pp. Livingstone. Edinburgh. 1974.

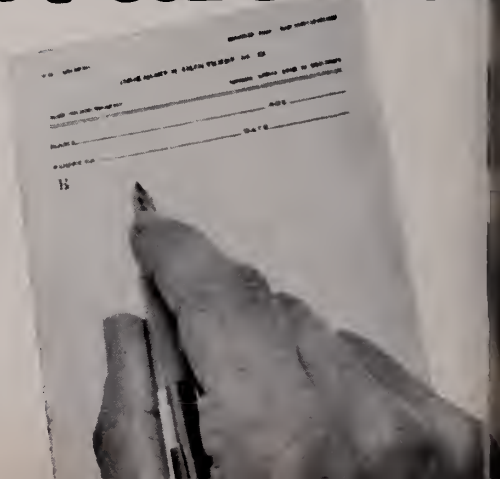
This is the tenth edition of a popular text on physical diagnosis written by a Scottish physician for a British audience. Americans will understand and appreciate the language but would prefer a less insular data base. All statistics are from the UK.

There are many ways to study a disease, for instance reading the description of a particular illness in a medical textbook. But diseases don't present as textbook pictures. Seward ably presents the development of a case study starting from the symptoms and signs that bring the patient to the doctor. The work suffers from a total lack of illustrations. References to authors are given with no specific bibliographic note. The book is octavo, weighs 1¾ lbs, measures 5 x 10 x 1 inch, just right for an English house officer's pocket and recommended for anyone who speaks the language.

Reuben Berman, M.D.
Editor Emeritus



Bioequivalenc



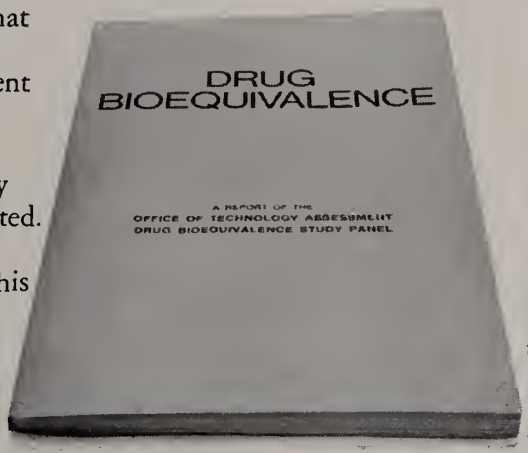
ıe weight of scientific opinion:

If the pharmacist substituted a ıically equivalent drug for the ou have specified for your nt—could you be certain of that uct's safety and effectiveness ly because the chemical content he same?

Definitely not, unless bio- valence tests and other quality ance checks had been conducted. pharmaceutical industry and y scientists have maintained this ion for years, but others have tioned it. Now the Office of nology Assessment of the gress of the United States has rted on the issue in its Drug quivalence Study.*

Here are a few definitive state- ts in the O.T.A. report:

"...the problem of bioinequiva- y in chemically equivalent prod- is a real one. Since the studies in h lack of bioequivalence was onstrated involved marketed ucts that met current compen- standards, these documented in- es constitute unequivocal ence that neither the present dards for testing the finished uct nor the specifications for rials, manufacturing process, controls are adequate to ensure that ostensibly equivalent drug products are, in fact, equivalent in bioavailability.



"While these therapeutic failures resulting from problems of bioavailability were recognized and well documented, it is entirely possible that other therapeutic failures and/or instances of toxicity that had a similar basis have escaped attention."

The Pharmaceutical Manufacturers Association supports federal legislative amendments that would require manufacturers of duplicate prescription pharmaceutical products, subject to new drug procedures, to document:

(a) chemical equivalence; and

(b) biological equivalence, where bioavailability test methods have been validated as a reliable means of assuring clinical equivalence; or

(c) where such validation is not possible, therapeutic equivalence.

In addition, the PMA supports federal legislation that would require certification of all manufacturers of prescription products before they could start in business, annual inspections and certification thereafter, and strict adherence to FDA regulations on good manufacturing practices.

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Washington, D.C. 20005

*Copies of the complete report on Drug Bioequivalence may be obtained from the Superintendent of Documents, U.S. Government Printing Office, Washington, D.C. 20402.

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He faded, and so calm and meek,
So softly worn, so sweetly weak,
So tearless, yet so tender, kind,
And grieved for those he left behind;
With all the while a cheek whose bloom
Was as a mockery of the tomb,
Whose tints as gently sunk away
As a departing rainbow's ray;
An eye of most transparent light,
That almost made the dungeon bright.*

*Lord Byron: The Prisoner of Chillon.

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Contraindications: Patients with known ypersensitivity to the drug.

Warnings: Caution patients about possible ombined effects with alcohol and other CNS epressants. As with all CNS-acting drugs, aution patients against hazardous occupa- ons requiring complete mental alertness e.g., operating machinery, driving). Though hysical and psychological dependence have arely been reported on recommended doses, se caution in administering to addiction- rone individuals or those who might increase osage; withdrawal symptoms (including onvulsions), following discontinuation of the rug and similar to those seen with barbitu- ates, have been reported. Use of any drug in regnancy, lactation, or in women of child- earing age requires that its potential benefits e weighed against its possible hazards.

Precautions:

ORAL: In the elderly and debilitated and in hildren over six, limit to smallest effective osage (initially 10 mg or less per day) to reclude ataxia or oversedation, increasing radually as needed and tolerated. Not recom- ended in children under six.

INJECTABLE: Keep patients under observa- on, preferably in bed, up to three hours after itial injection; forbid ambulatory patients to perate vehicle following injection; do not dminister to patients in shock or comatose tates; use reduced dosage (usually 25 to 50 ng) for the elderly or debilitated and for hildren age twelve or older.

ORAL AND INJECTABLE: Though generally ot recommended, if combination therapy ith other psychotropics seems indicated, arefully consider individual pharmacologic ffects, particularly in use of potentiating ompounds such as MAO inhibitors and henothiazines. Observe usual precautions in resence of impaired renal or hepatic func- on. Paradoxical reactions (e.g., excitement, timulation and acute rage) have been eported in psychiatric patients and hyper- ctive aggressive children. Employ usual



precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.

With the injectable form, isolated instances of hypotension, tachycardia and blurred vision have been reported; also hypotension associated with spinal anesthesia, and pain following I.M. injection.

Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral: Adults:* Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)

For Parenteral Administration: Should be individualized according to diagnosis and response. While 300 mg may be given during a 6-hour period, do not exceed this dose in any 24-hour period. To control acute conditions rapidly, the usual initial adult dose is 50 to 100 mg I.M. or I.V. Subsequent treatment, if necessary, may be given orally. (See Precautions.)

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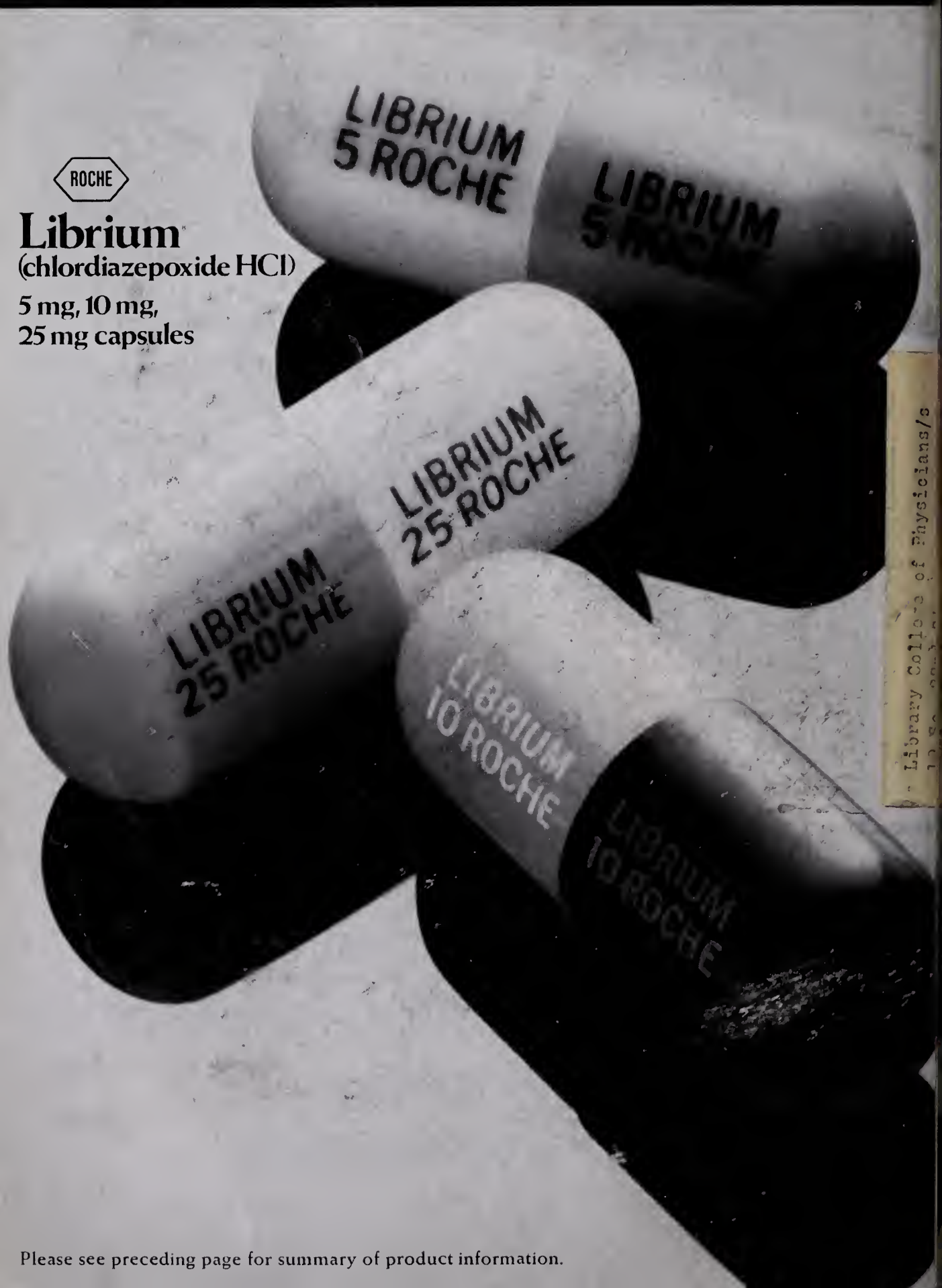
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Please see following page.

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Library Colle-e of Physicians/s

Please see preceding page for summary of product information.

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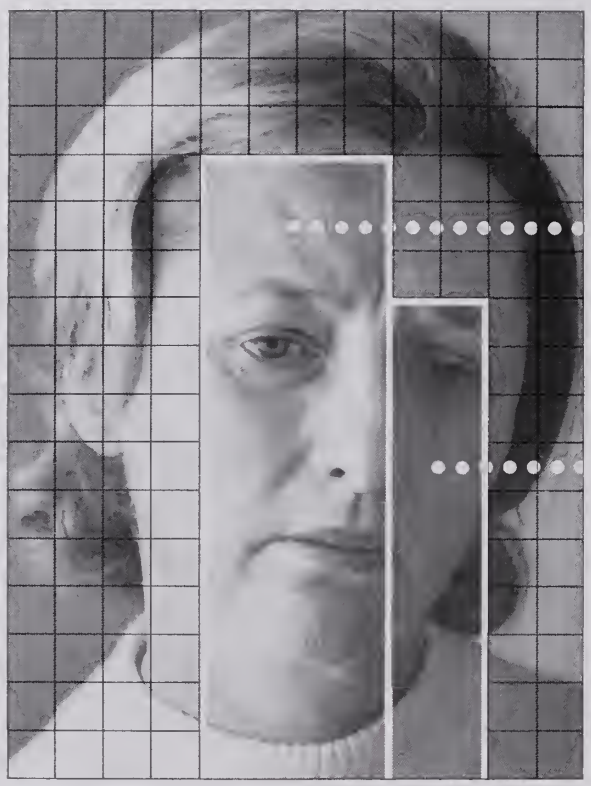
"...ite Valley" — *J. W. Burnett, M.D.*

AUGUST 1975

Proceedings of the Symposium on
Community Control of Streptococcal
Infections

Special Issue

Both often



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Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in freq and/or severity of grand mal seizure require increased dosage of standar convulsant medication; abrupt with may be associated with temporary i crease in frequency and/or severity seizures. Advise against simultaneo gestion of alcohol and other CNS de sants. Withdrawal symptoms (simil those with barbiturates and alcohol occurred following abrupt discontin (convulsions, tremor, abdominal an cle cramps, vomiting and sweating) addiction-prone individuals under c

respond to one

According to her major
mptoms, she is a psychoneu-
ic patient with severe
kiety. But according to the
cription she gives of her
elings, part of the problem
y sound like depression.
is is because her problem,
hough primarily one of ex-
sive anxiety, is often accom-
nied by depressive symptom-
logy. Valium (diazepam)
provide relief for both—as
excessive anxiety is re-
ed, the depressive symp-
ns associated with it are also
en relieved.

There are other advan-
es in using Valium for the
nagement of psychoneu-
ic anxiety with secondary
pressive symptoms: the
chotherapeutic effect of
lium is pronounced and
id. This means that im-
vement is usually apparent
in the patient within a few days rather than in a week or two, although it may take longer in some patients. In addition, Valium (diazepam) is generally well tolerated; as with most CNS-acting agents, caution patients against hazardous occupations requiring complete mental alertness.

Also, because the psychoneurotic patient's symptoms are often intensified at bedtime, Valium can offer an additional benefit. An *h.s.* dose added to the *b.i.d.* or *t.i.d.* treatment regimen can relieve the excessive anxiety and associated depressive symptoms and thus encourage a more restful night's sleep.



Valium® (diazepam)

2-mg, 5-mg, 10-mg tablets

in psychoneurotic
anxiety states
with associated
depressive symptoms

rveillance because of their predisposi-
n to habituation and dependence. In
egnancy, lactation or women of child-
aring age, weigh potential benefit
ainst possible hazard.

ecautions: If combined with other psy-
otropics or anticonvulsants, consider
refully pharmacology of agents em-
oyed; drugs such as phenothiazines,
rcotics, barbiturates, MAO inhibitors
d other antidepressants may potentiate
action. Usual precautions indicated in
tients severely depressed, or with latent
pression, or with suicidal tendencies.
Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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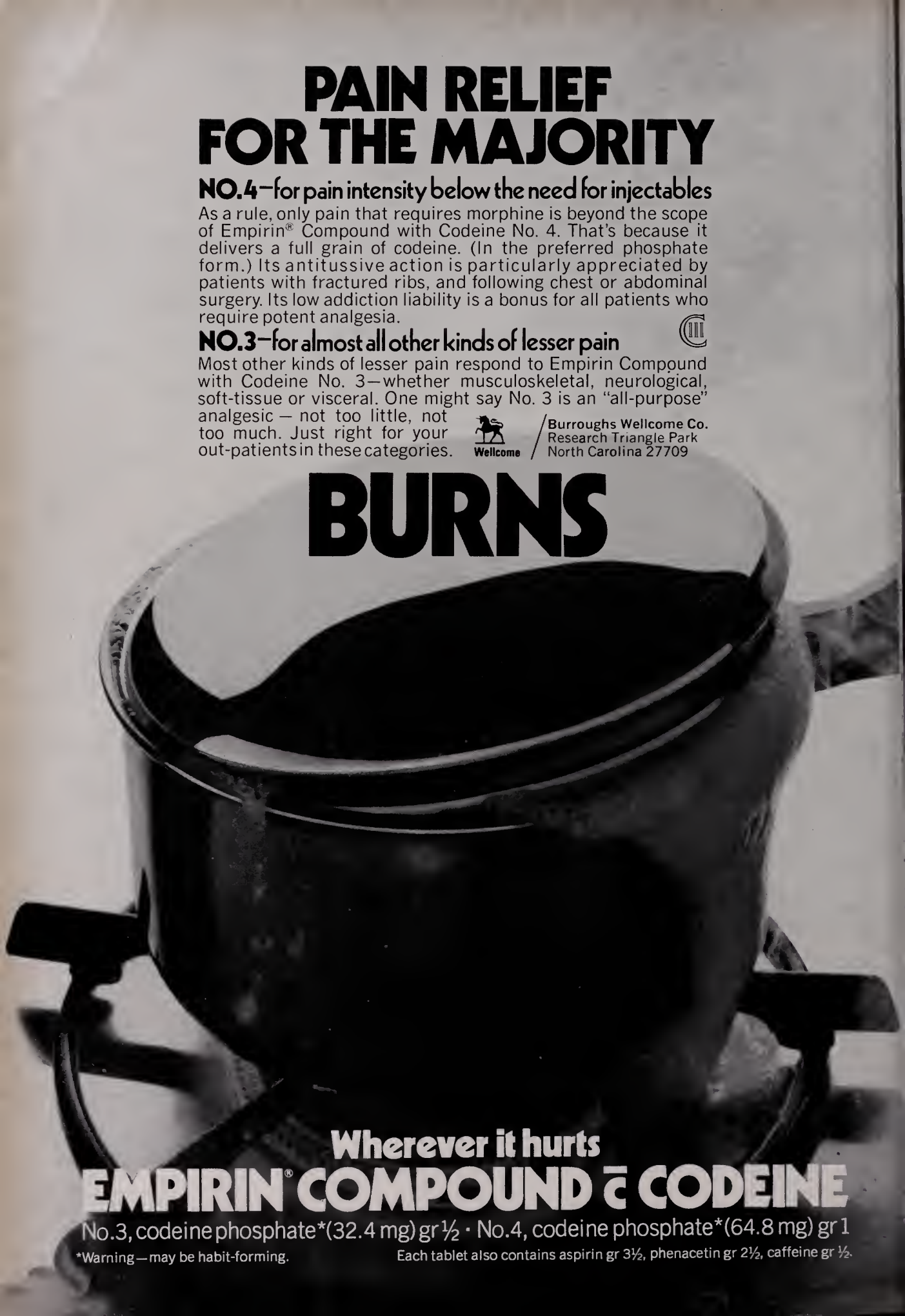
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President's Letter



Unreasonable Expectations

Multiple factors contribute to the current medical professional liability crisis. A significant factor, rarely mentioned, is the unreasonable expectations of some patients. The medical profession which has dealt so successfully with post-graduate and continuing education of physicians in the past ten years appears unable to deal effectively with the problems of individual patient education. And patient education appears to be the simple and logical way to avoid unreasonable expectations in diagnosis and treatment.

Even though our patients are more knowledgeable and sophisticated medically, patient education programs have marked variability in quality. Not uncommonly much of the patient's medical knowledge is, in fact, misinformation and misinterpretation. Medical journalism and reporting in the communications media often deal with complex medical problems superficially or sensationally and the medical information is often written and reported without the medical profession's input or review. For example, the television programs that cast the physician in the role of a superman performing miracles of diagnosis and cure do little to educate the patient and frequently aggravate the patient's unreasonable expectations for solutions to his own medical problems. I believe such programs are a disservice to medicine and are to be deplored even though there is a strong temptation for each of us to bask in the reflected glory of the portrayal of such improbable heroes of medicine.

The public health education programs sponsored and supported by medical societies and health departments are excellent sources of health information and education for the public. The Minnesota State Medical Association does an excellent job in this field of public health education with its many programs. The real problem, however, is with the one to one, physician to patient, communication. The physician must allow enough time in his too busy schedule for patient education. The best public relations of the doctor's practice is good patient education. An informed patient will be a pleased patient and the pleased patient rarely brings charges of malpractice. The patient's expectations will be reasonable when based on sound medical experience and information with the variabilities and probabilities of diagnosis and treatment honestly appraised. The physician must look to himself to correct this factor contributing to the crisis in medical professional liability.

G. Roy Diessner, M.D.
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Minnesota State Medical Association

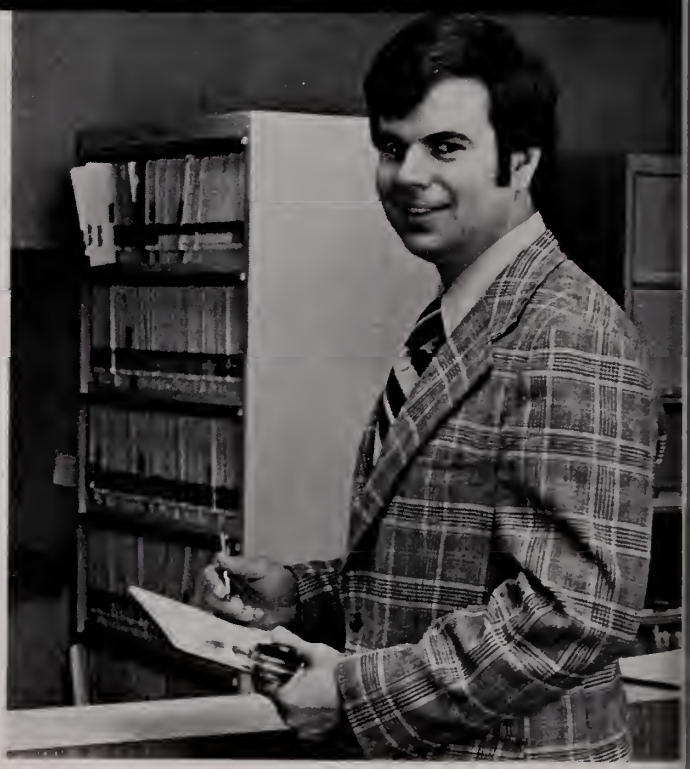
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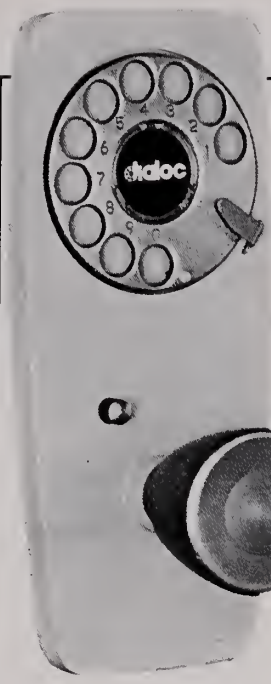
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farmed out

dear doctors
my boss the editor
has left the city
to go to his farm
he says open spaces
restore his sense
of proportion and
the change of pace
helps him concentrate
anyway whatever
his excuses
he put me in charge
of this editors page
which is a good thing
because this issue
concerns the streptococcus
and it is about time
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more space to the
smaller things of life
after all it is
the microorganisms
that form the foundation
of all living things and
really make the universe go
if humans spent more time
thinking small
they would realize
their relative insignificance
among the spinning stars
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control August
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- Necrotic Tissue and Associated Odor

HELPS PREPARE WOUND FOR:

- Granulation/Healing
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CLEANSE WOUND
Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials.



THOROUGHLY MOISTEN
Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g., sodium chloride or water solutions).



APPLY ENZYME
Apply a layer of TRAVASE Ointment. Assure intimate contact with necrotic tissue and complete wound coverage.

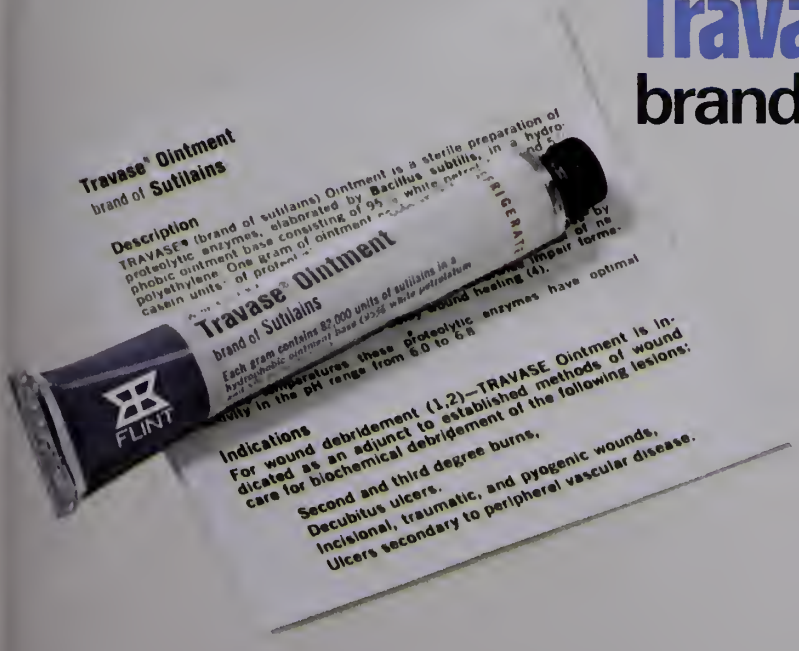


APPLY MOIST DRESSING
Apply loose moist dressings (most important with dry leathery eschar).



CHANGE DRESSINGS
When changing dressing, gently wipe away the dissolved material. Repeat the procedure, including application of TRAVASE Ointment, 3 to 4 times per day for best results.

Travase® Ointment
brand of Sutilains



FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC
Deerfield, Illinois 60015

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Travase® Ointment brand of Sutilains

ulcers

TERRY V. CARLE, M.D., CLINICAL INSTRUCTOR, DEPT. OF PHYS. MED. & REHAB., CRAIG REHABILITATION HOSPITAL, UNIVERSITY OF COLORADO



Before treatment, necrotic matter coated the inner surfaces of this decubitus ulcer.



After nine days of TRAVASE therapy, debridement is nearly complete and granulation evident.

burns

DALE B. DUBIN, M.D., DIPLOMATE, AMERICAN BOARD OF PLASTIC SURGERY, TAMPA, FLORIDA



Before treatment . . .



48 hours following treatment with TRAVASE Ointment on right hand; left hand is control.

Travase® Ointment

(brand of Sutilains)

Indications: For wound debridement, TRAVASE Ointment is indicated as an adjunct to established methods of wound care for biochemical debridement of the following lesions:

- Second and third degree burns,
- Decubitus ulcers,
- Incisional, traumatic, and pyogenic wounds,
- Ulcers secondary to peripheral vascular disease.

Contraindications: Application of TRAVASE Ointment is contraindicated in the following conditions:

- Wounds communicating with major body cavities,
- Wounds containing exposed major nerves or nervous tissue,
- Fungating neoplastic ulcers,
- Wounds in women of child-bearing potential—because of lack of laboratory evidence of effects of TRAVASE upon the developing fetus.

Warning: Do not permit TRAVASE Ointment to come into contact with the eyes. If contact is made, immediately rinse with copious amounts of water, preferably sterile.

Precautions: A moist environment is essential to optimal activity of the enzyme. Enzyme activity may also be impaired by certain agents (see package insert). Although there have been no reports of systemic allergic reaction in humans, studies have shown that there may be an antibody response in humans to absorbed enzyme material.

Adverse Reactions: Consist of mild, transient pain, paresthesias, bleeding and transient dermatitis. Pain usually can be controlled by administration of mild analgesics. Side effects severe enough to warrant discontinuation of therapy occasionally have occurred.

If bleeding or dermatitis occurs as a result of the application of TRAVASE Ointment, therapy should be discontinued. No systemic toxicity has been observed as a result of the topical application of TRAVASE Ointment.

DOSAGE AND ADMINISTRATION: STRICT ADHERENCE TO THE FOLLOWING IS REQUIRED FOR EFFECTIVE RESULTS OF TREATMENT:

1. Thoroughly cleanse and irrigate wound area with sodium chloride or water solutions. Wound MUST be cleansed of antiseptics or heavy-metal antibacterials which may denature enzyme or alter substrate characteristics (e.g., hexachlorophene, silver nitrate, benzalkonium chloride, nitrofurazone, etc.).
2. Thoroughly moisten wound area either through tubbing, showering, or wet soaks (e.g. sodium chloride or water solutions).
3. Apply TRAVASE Ointment in a thin layer assuring intimate contact with necrotic tissue and complete wound coverage extending ¼ to ½ inch beyond the area to be debrided.
4. Apply loose wet dressings.
5. Repeat entire procedure 3 to 4 times per day for best results.

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DIVISION OF TRAVENOL LABORATORIES, INC
Deerfield, Illinois 60015

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Streptococcology for the Non-Streptococcologist*

ANGELO TARANTA, M.D.*

Basic information on streptococci is presented for the benefit of the uninitiated. These interesting organisms are portrayed primarily as villains, or agents of diseases, with apologies to other streptococci, which help make tasty cheeses.

RECENTLY MY father-in-law, a 93-year-old electrical engineer, asked me what a streptococcus is, and in which way, if any, it differs from a staphylococcus or a pneumococcus. In the preceding 23 years of our acquaintance, he had never asked me this question, despite a not-so-vague awareness that I had made of the streptococcus, if not exactly a career, certainly a hobby.

Introducing the Streptococci: What They Do, How They Look

The reason he asked me that question was that his 78-year-old wife had been reported to have a blood culture positive for Gram-positive cocci. He had looked up these words in a pocket encyclopedia and from there he had moved to the larger expanses of the *Webster Third New International Dictionary* which, under streptococcus, reads:

> A genus of non-motile chiefly parasitic Gram-positive bacteria that divide in only one plane, occur in pairs or chains but not in packets . . . and include various important pathogens of man and domestic animals as well as other organisms important as starters in the manufacture of dairy products.

These are the reasons why people became interested in streptococci: diseases, on one hand, and cheese, on the other.

My Father-in-law was not satisfied with the purely verbal description of the *Webster*, and asked me to draw a picture. Here it is: (Figure 1).

The propensity of streptococci to divide in only one plane determines their arrangement in pairs or chains, which in turn has determined their name, since *cocci* means round organisms, and *"strepto"*, from the Greek, indicates that they are arranged in chains, as in a necklace. They thus

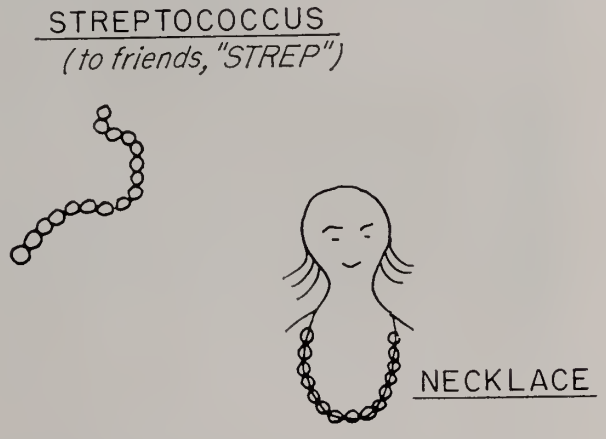


Fig. 1—Artist's rendering of a chain of streptococci, with object from which their name derived.

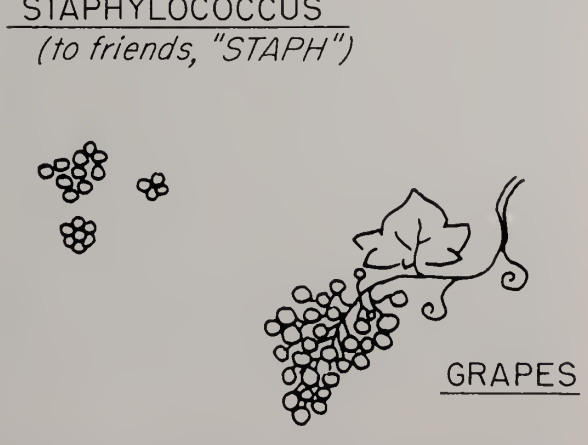


Fig. 2—Artist's rendering of a cluster of staphylococci, with object from which their name derived.

*Departments of Medicine, New York University School of Medicine, and Cabrini Health Care Center, New York City.
Address reprint requests to: Cabrini Health Care Center, 227 E. 19th St., New York, NY 10003.
Presented at the Symposium on Community Control of Streptococcal Infections held in Minneapolis, Minnesota, June, 1974.

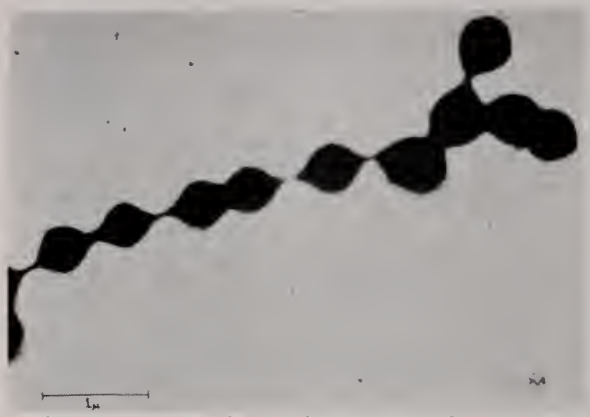


Fig. 3—Electron photomicrograph of *S. pyogenes* showing persistence of intercellular bridges causing chain formation. (From S. Mudd and D. B. Lockman, J Bact 41:415, 1941. Permission granted.)

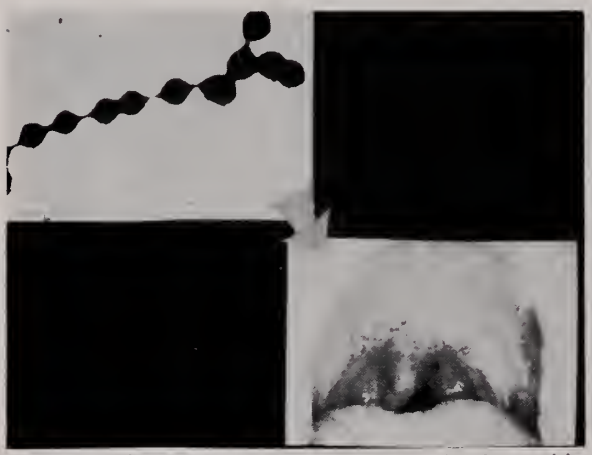


Fig. 4—Streptococci and streptococcal pharyngitis. (Upper left photograph from S. Mudd and D. B. Lockman, J Bact 41:415, 1941. Lower right photograph courtesy of Dr. Milton Markowitz. Permission granted.)

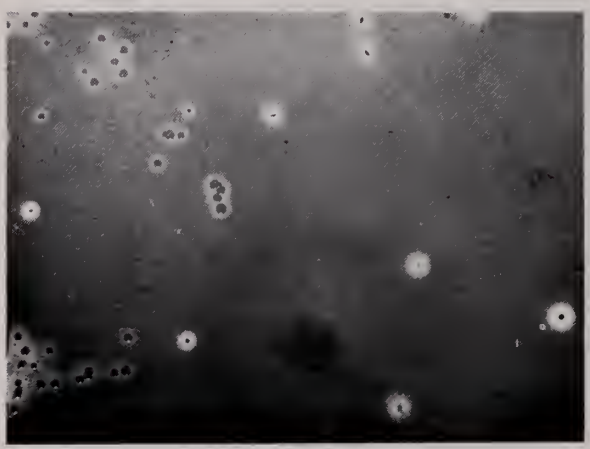


Fig. 5—Streptococcal colonies growing on the surface of a blood agar plate as well as deep into it. Notice the larger halo of hemolysis surrounding the deep colonies. (Courtesy of National Medical Audiovisual Center, Atlanta, Georgia. Permission granted.)

differ from staphylococci (Figure 2), which divide along multiple planes, and therefore assemble in packets or clusters not unlike grapes (*"staphylos"* means grape in Greek).

Figure 3 is a more realistic picture of a streptococcal chain. It is one of the earliest electron micrographs of streptococci, which demonstrates their necklace-like arrangement. I selected this picture also because of its subtly ominous, dragon-like quality. In Figure 4, I have connected this same picture by an arrow to the picture of a strep throat or streptococcal pharyngitis. As I'm sure the other contributors to this symposium will make clear, a "strep throat" is not always very sore, and may be not sore at all. In fact, there is no clinical sign or constellation of signs and symptoms that allow physicians to diagnose it without the aid of a throat culture.

Throat Culture

A throat culture can accurately reveal whether the streptococci that cause rheumatic fever and most cases of nephritis, *beta-hemolytic streptococci,* are present. If they are present, areas of complete clearing and discoloration will appear in the otherwise red and opaque blood-agar mixture used as a culture medium around small translucent or whitish colonies of streptococci. This clearing around the colonies gives these streptococci their names—*hemolytic* streptococci—meaning that they are capable of breaking down red cells. The lysis of red cells is caused by two products the streptococci put out, streptolysin O and streptolysin S—O standing for oxygen labile,



Fig. 6—A beta-hemolytic streptococcal colony growing under the surface of a blood agar plate. Notice the area of hemolysis, which is complete and starts right at the edge of the colony. (Courtesy of National Medical Audiovisual Center, Atlanta, Georgia. Permission granted.)

that is, susceptible to inactivation by oxygen. Hemolysis is more complete when oxygen is scarce, because then both hemolysins are active. This is illustrated in Figure 5, where on the same blood-agar plate can be seen streptococcal colonies growing on the surface, where oxygen is plentiful, as well as deep in the agar, where it is scarce.

Figure 6 is a blow-up of a single sub-surface colony surrounded by a striking area of hemolysis. The hemolysis starts at the edge of the colony, and is complete. For comparison, Figure 7 illustrates a colony of non-hemolytic streptococci, which are less pathogenic for man, and do not cause rheumatic fever or acute glomerulonephritis. The surface of streptococcal colonies isolated from epidemics is often glistening, when the colonies are young (Figure 8). On further incubation, the colonies shrink and acquire a dull surface—a characteristic which has also been associated with epidemic strains and virulence. Both the gilstening and the subsequent dull appearance of the colonies is due to a capsule of hyaluronic acid surrounding each organism, as seen best in India ink preparations (Figure 9).

It is unfortunate that the presence of streptococci in the throat does not, by itself, indicate an active infection. Streptococci may linger in the throat for months after the acute stage of a streptococcal infection. Definitive proof of infection comes only from rising titers of streptococcal antibodies. Since antibody titers may require two to three weeks to rise, their determination is of no help in deciding which patient to treat. After the acute initial stage of the infection they are of



Fig. 7—A non-hemolytic streptococcal colony growing under the surface of a blood agar plate, surrounded by non-hemolyzed red cells. Contrast with Figure 6, (Courtesy of National Medical Audiovisual Center, Atlanta, Georgia. Permission granted.)



Fig. 8—Young streptococcal colonies growing on the surface of the plate. Notice the glistening surface, characteristic of some highly virulent strains, and due to the production of a hyaluronic acid capsule. (From A. T. Wilson, J Exp Med 109:257, 1959. Permission granted.)

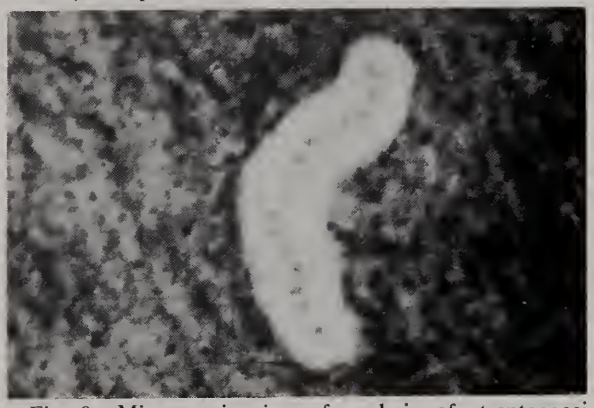


Fig. 9—Microscopic view of a chain of streptococci surrounded by a hyaluronic acid capsule. The capsule is visualized by contrast with the India ink surrounding it. (From Sidney Rothbard, J Exp Med 88:325, 1948. Permission granted.)

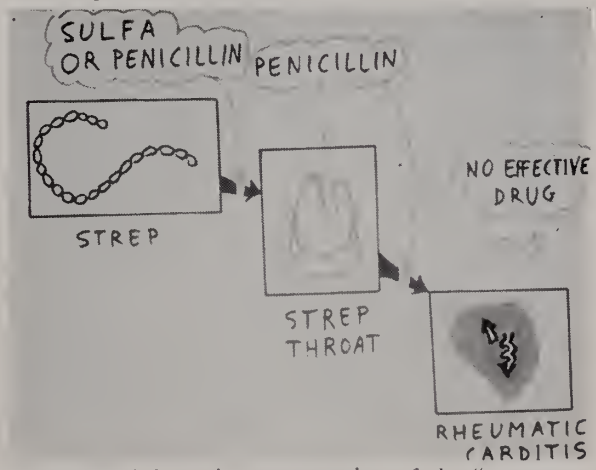


Fig. 10—Schematic representation of the "streptococcal cascade". Streptococcal infections can be prevented by continual administration of sulfa or of penicillin, and rheumatic fever can be prevented by treatment of streptococcal infections with penicillin (but not with sulfa). Once rheumatic fever starts, including carditis, treatment is ineffective.



Fig. 11—Electron photomicrograph of group A streptococcal cell walls extracted with hot formamide. Residue structures seen in micrograph are composed of mucopeptide. X Ca 15,000. (From E. H. Freimer, R. M. Krause, and M. McCarty: J Exp Med 110:853, 1959. Permission granted.)

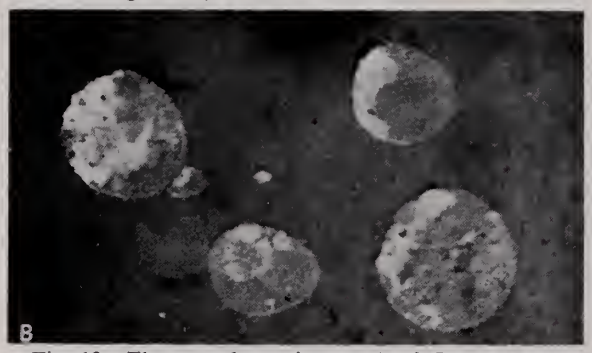


Fig. 12—Electron photomicrograph of Group A streptococcal cell membranes. (From E. H. Freimer, R. M. Krause, M. McCarty: J Exp Med 110:853, 1959. Permission granted.)

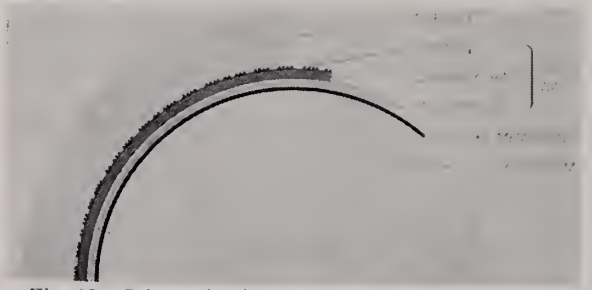


Fig. 13—Schematic diagram of the anatomy of a streptococcal cell. (From E. H. Freimer and M. McCarty, Scientific American 213:66, 1965. Permission granted.)

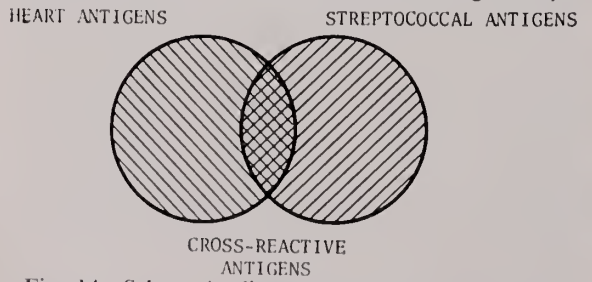


Fig. 14—Schematic diagram showing the relation of streptococcal antigens to heart antigens. The immune reaction elicited by streptococcal infections is directed in part also against heart antigens.

help, however, as an aid in diagnosing the sequels of streptococcal infections, rheumatic fever and acute glomerulonephritis, because neither occurs without a rise of streptococcal antibodies.

A First Recapitulation

Figure 10 summarizes the first part of this presentation, highlighting the sequence, or cascade, of events: the streptococci, streptococcal pharyngitis, and rheumatic carditis, certainly the most important manifestation of rheumatic fever. In addition, the figure highlights the useful applications of this knowledge: streptococcal infections can be prevented by continual administration of sulfa or of penicillin, and rheumatic fever, including carditis, can be prevented if penicillin, but not sulfa, is administered in appropriate manner during the course of a streptococcal infection. Once carditis starts, however, there are no curative drugs.

A Closer Look into How the Strep Looks

Like the other bacteria and like the cells of plants, the streptococci have a rigid cell wall which can be isolated by mechanical disruption, enzymatic treatment, and differential centrifugation, as in this photograph by Freimer, Krause and McCarty (Figure 11). Underneath the rigid cell wall, streptococci have, so to speak, a second skin, which is softer and pliable and is like the plasma membrane of mammalian cells (Figure 12). This is called the streptococcal cell membrane. Both of these structures, the rigid outer cell wall and the soft inner cell membrane, may be important in

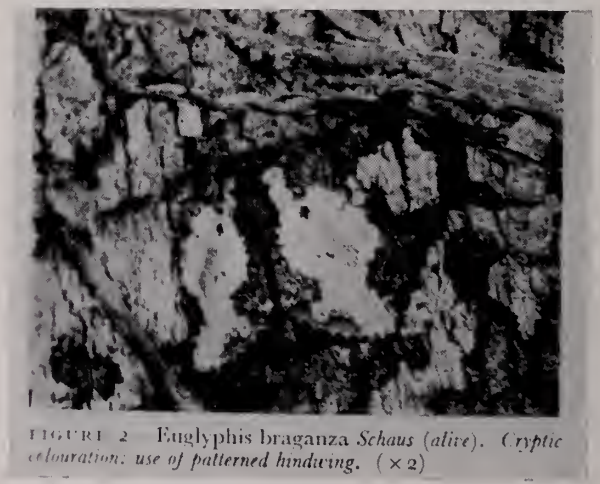


FIGURE 2 Euglyphis braganza *Schaus (alive). Cryptic colouration: use of patterned hindwing.* (×2)

Fig. 15—Tropical moth with wing markings similar to the pattern of the bark on which it rests. Classic example of protective coloration or mimicry. (From Kettlewell, H. B. D., Endeavor 18:200, 1959. Permission granted.)

the pathogenesis of streptococcal and post-streptococcal disease—the cell wall because it is difficult to digest and dispose of, and the cell membrane because it resembles mammalian plasma membranes, so that an immune response against the streptococcal cell membrane might damage the mammalian plasma membrane.

Figure 13 illustrates in a diagrammatic manner the full anatomy of the streptococcal cell, as it is presently understood, and including the components previously shown in isolation. Going from the outside to the inside we encounter the hyaluronic acid capsule—in the case of encapsulated, highly virulent, epidemic strains. Immediately under the capsule, if one is present, is a discontinuous layer of protein, of which more later. And under it, in succession, are the carbohydrate and mucopeptide layers of the cell wall. The nature of the carbohydrate determines the serologic group: A, B, C, etc. Only Group A organisms are capable of causing rheumatic fever or acute glomerulonephritis. Still further inward is the cell membrane, which immediately envelops the cytoplasm.

Strep and Man: How Similar They Are

Much has been made of the reported immunologic cross-reactions between streptococcal and mammalian cell components (Figure 14) to explain the pathogenesis of post-streptococcal diseases—rheumatic fever and acute glomerulonephritis. This phenomenon of immunologic mimicry may be the counterpart of the well-known morphologic mimicry of insects and other animals who, in the course of evolution, have acquired a protective coloration (Figure 15). In rheumatic fever we have been confronted with an embarrassment of riches, as a multitude of streptococcal products have been shown to correlate with human antigens in the heart and elsewhere, but their pathogenetic role, if any, remains uncertain. In acute glomerulonephritis, also, cross-reactions have been described between streptococcal cell components and kidney tissue antigens, but the typical granular or "lumpy-bumpy" pattern of deposition of gammaglobulin on the basement membrane of the renal glomeruli (Figure 16) suggests that antigen-antibody complexes circulating in the blood stream and secondarily deposited in the kidney glomeruli are responsible for the glomerular damage. Cross-reacting anti-kidney antibodies would give a smooth or linear pattern of deposition, like Goodpasture's syndrome, and unlike the granular pattern shown here and typical of post-streptococcal nephritis.

M Proteins and Fimbriae

It has been known for a long time that a family of protein antigens closely associated with virulence—the M proteins—is located on the outer side of the cell wall. These proteins interfere with phagocytosis and antibodies against them overcome the interference, thus protecting against streptococcal infections of the homologous type. More recently, electron micrographs of thin sections of streptococcal cells have provided direct morphologic support of this concept. Swanson has shown that M proteins are associated with hair-like structures similar to cilia of other bacteria, but not motile, which are called fimbriae (Figure 17). Still more recently, workers at the Harvard School of Dental Medicine have shown that fimbriae facilitate the primary attachment of the streptococcal cells to mammalian epithelial cells. Thus, they are instrumental in the inial attachment of streptococci to the throat, the necessary first step in colonization and infection.

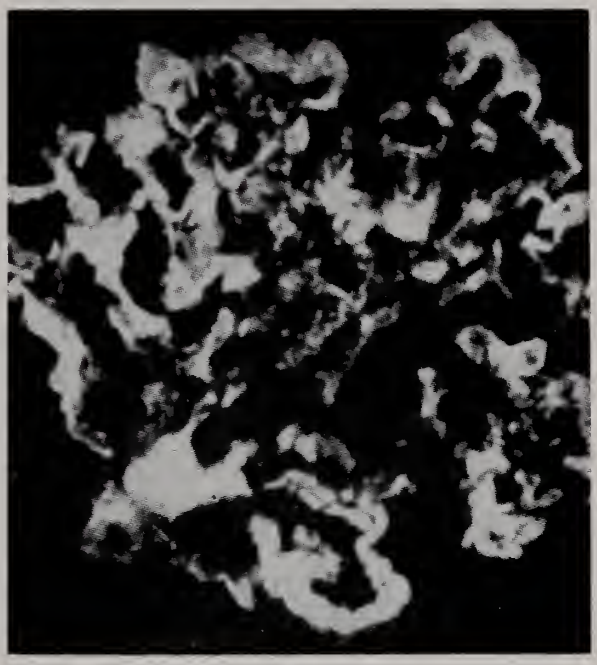


Fig. 16—Granular deposits of gamma G globulin in glomerulus of renal biopsy of patient with poststreptococcal acute glomerulonephritis. This granular pattern is characteristic of immune complex nephritis, of which acute post-streptococcal glomerulonephritis is the human prototype. (From M. H. Kaplan in Acute Glomerulonephritis edited by J. Metcoff, Little Brown & Co., Boston, pp. 69. Permission granted.)

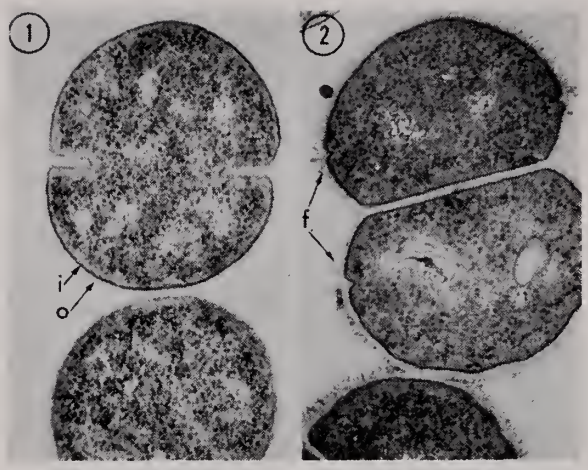


Fig. 17—Streptococcal cells devoid of M protein (1) and endowed with it (2). The M protein is located in the fimbriae, visible only in (2) (F). I and O indicate the inner and outer layer of the cell wall. (From J. Swanson, K. C. Hsu, and E. C. Gotschlich, J Exp Med 130:1063, 1969. Permission granted.)

What the Strep Puts Out

In addition to the cellular components, the streptococci excrete a wide variety of extracellular products. Initially such products became known because of their distinctive toxic or enzymatic effects—like streptolysin O and S, which I have mentioned already, hyaluronidase, and erythrogenic toxin, which is responsible for the rash of *scarlet fever*—a special kind of streptococcal sore throat. Additional extracellular products are capable of digesting protein (streptococcal proteinase), and of degrading DNA (streptococcal deoxyribonucleases). More recently, immunologic analysis has been applied to the study of these extra-cellular products, (Figure 18). The complexity of the pattern indicates the multitude of antigenic streptococcal extra cellular products, since each line indicates an immunologically distinct streptococcal product. A number of these extracellular products remain unidentified in terms of function.

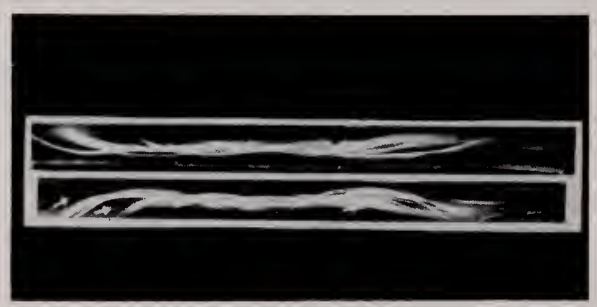


Fig. 18—Immunoelectrophoretic pattern of streptococcal extracellular antigens developed with 16% solution of pooled human immunoglobulins. Upper and lower antigen wells are filled with crude concentrates of streptococcal culture filtrates obtained from the same streptococcal strain; the arrows indicate two minor antigenic components present in only one of the filtrates, indicating how minor environmental changes difficult or impossible to track down may result in variations in extracellular products. (From S. M. Halbert and S. L. Keatinge, J Exp Med 113:1016, 1961. Permission granted.)

Speculations

It is intriguing to speculate why the streptococcal cell cross-reacts immunologically with the cells of its hosts. Zabriskie has advanced the hypothesis that this similarity may represent a protective mechanism whereby the streptococci can elude, at least in part, the immune response of the host, by fading, so to speak, into the host's immunologic background.

As an accidental byproduct of this mimicry, the pathogenetic potential of streptococci may be increased, since the immune response directed against them may backfire and damage the cell components of the host, some of which are immunologically similar to the cell components of the parasite. Though attractive, this hypothesis is supported only by indirect and non-rigorous evidence. In fact, it may prove very difficult to validate this hypothesis experimentally, since no reliable experimental model of rheumatic fever has yet been described, and the notion of direct, provocative experiments in man dismisses itself.

So much for the streptococcus, and for my introductory guided tour to streptococcus country. We do not yet know it intimately, but have defined it and are developing an acquaintance with it. As for streptococcologists, they are of course much more difficult to define, being way more complicated organisms. Luckily *their* definition was not my assignment.

Summary

The investigation of streptococci has yet to yield its ultimate dividend: that intimate understanding of the pathogenesis of rheumatic fever from which we hope a cure may derive. In the meantime, a few basic facts have been ascertained

beyond doubt: there is no rheumatic fever or the garden variety of acute glomerulonephritis without a preceding streptococcal infection; treatment of streptococcal infections prevents rheumatic fever, and prophylaxis of streptococcal infections eliminates the risk of recurrences of rheumatic fever. Perhaps, should our will be strong and funds be available, this is all we need to know to eradicate these diseases.

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Minnesota Department of Health and Minnesota Heart Association to Perform Study of Acute Rheumatic Fever in Minnesota

During the next 10 months, the Minnesota Department of Health and the Minnesota Heart Association will be coordinating a study of acute rheumatic fever trends in the State. This study, to be done with the assistance of several pediatric cardiologists in different areas of Minnesota, is the first part of an effort to better define the current incidence of acute rheumatic fever in the state.

The plan of the study is as follows. When patients under age 20 with onset of acute rheumatic fever during the previous four months are reported to the rheumatic fever registry of the Minnesota Department of Health, a pediatric cardiologist participating in the study will be notified. He or she will then contact the patient's primary physician to obtain additional clinical, laboratory, and epidemiologic information on the case. All information on individual cases will be kept confidential and used only for the purpose of this study. A summary of results and conclusions of this study will be distributed to all physicians in the state.

This study has been endorsed by the Council, the Heart Committee, and the Child Health Committee of the Minnesota State Medical Association. Questions, comments, or requests for additional information should be directed to Barry S. Levy, M.D., Minnesota Department of Health, 717 Delaware Street S.E., Minneapolis, MN 55440. All physicians are encouraged to report suspect cases of acute rheumatic fever or rheumatic heart disease to the Minnesota Department of Health registry, and thereby make such patients eligible for receiving prophylactic antibiotics at reduced cost. Provision of such medications takes place under the Rheumatic Fever Secondary Prevention Program, sponsored by the Minnesota State Medical Association, the Minnesota Department of Health, the Minnesota Heart Association, and the Minnesota Pharmaceutical Association.

Epidemiology and Pathogenesis of Acute Rheumatic Fever

Recent Concepts

EDWARD L. KAPLAN, M.D.*

Current data suggest that although the incidence and severity of acute rheumatic fever has decreased in the United States during the last several decades, this nonsuppurative sequel of group A streptococcal respiratory tract infections continues to occur at an unacceptable rate. However, the available figures may not accurately reflect the actual incidence due to the inadequacies of present methods for reporting rheumatic fever.

The mechanisms responsible for development of rheumatic fever and rheumatic heart disease still remain an enigma. Hypotheses to explain the pathogenesis of this sequel of streptococcal infection include not only direct group A streptococcal infection of the valves, but also toxic effects of streptococcal extracellular products, immune mechanisms, and basic differences in the biological characteristics of some strains of streptococci.

Until the exact pathogenetic mechanisms responsible for the development of this disease are understood, the prevention of rheumatic fever will remain entirely dependent upon control of streptococcal infections.

Control of streptococcal infections and acute rheumatic fever relies upon the results of over three decades of intense study. Contrary to the opinions of some, the introduction of antibiotics—especially penicillin—has not solved the problem, even in those countries with advanced standards of medical care. Many basic questions remain unanswered, although new information—from the laboratory scientist, from the epidemiologist and from the clinician—continually becomes available. These new data and re-evaluation of older data influence physicians and public health authorities in their approach to streptococcal infection and their sequelae. A review of some of the current concepts of the epidemiology and pathogenesis of acute rheumatic fever is therefore warranted.

Factors Influencing the Reported Incidence of Rheumatic Fever

For some time a decrease in both the incidence and in the severity of acute rheumatic fever in the United States has been recognized.[1] (This began even before the introduction of antibiotics into medical practice.) Table 1 is a summary of data from the rheumatic fever registry of the Minnesota State Department of Health demonstrating a decrease in the *reported* incidence of this disease in Minnesota during the past 10 years.[2] Is it that there are actually fewer cases occurring in Minnesota (and elsewhere) or is the apparent decrease influenced by incorrect application of the Jones Criteria and/or methods of reporting cases?

TABLE 1

New Cases of Rheumatic Fever and Rheumatic Heart Disease Reported to Minnesota Board of Health 1965-1973

Year	Cases Registered
1965	1069
1966	872
1967	769
1968	672
1969	590
1970	725
1971	596
1972	369
1973	374

*From the Department of Pediatrics, University of Minnesota School of Medicine, Minneapolis, Minnesota. Supported in part by the Dwan Family Fund.

Address for reprints: Dr. Edward L. Kaplan, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota 55455.

Presented at the Symposium on Community Control of Streptococcal Infections held in Minneapolis, Minnesota, June, 1974.

Errors in Reporting Rheumatic Fever

Current evidence suggests that the incidence of rheumatic fever may be highest among certain populations, especially economically and socially disadvantaged ones. The studies of Gordis and his colleagues in Baltimore confirm this by demonstrating that in urban areas clustering of cases occurs in the inner city.[3-4] In a recently completed study from a rural southwest area, similar incidence figures (about 16/100,000 population/year) were found among native American Indians.[5] For comparison, for the entire state of Minnesota figures obtained from the 1970 census and from the state rheumatic fever registry indicate that the incidence (based on reported cases) has varied during the last few years from 12-20/100,000 population/year.[2] (It is of interest that figures reported from one of the Scandinavian countries reveal a much lower incidence for acute rheumatic fever.[6])

In interpreting incidence data, one must realize that the methods of reporting rheumatic fever in the United States are probably quite inaccurate. During the early years of the Minnesota registry, for example, it was found that many cases seen by physicians went unreported to the registry.[7] Studies have also shown that only a fraction of the cases have been reported to the Maryland registry.[8] In Michigan it appears that many physicians in that state do not enroll their patients on the state registry and therefore many cases go unreported, perhaps as many as 25-50%.[9] On the other hand, it has been found in cases reported to the Minnesota state registry in the early 1960's that perhaps only half fulfilled the Jones Criteria.[10] Each of these types of errors not only influences the number of reported cases, but also tends to disguise the populations from which cases are drawn.

Data published recently by Roberts serve as another example of factors which may alter the accuracy of reported incidence figures.[11] This information, presented in a modified form in Table 2, suggests that isolated aortic valve disease is usually not rheumatic in origin. In the past many cases of aortic stenosis and insufficiency due to congenital bicuspid aortic valves (which has been reported by Campbell to occur in approximately 4/1000 live births[12]) were probably reported as rheumatic in origin. Thus, prior to the time when more careful diagnoses have been made by physicians using more sophisticated techniques, isolated aortic valve disease was probably frequently and incorrectly thought to be of rheumatic origin and registered as such. This error would tend to alter the slope of the decline in cases of rheumatic fever and rheumatic heart disease.

TABLE 2

Etiology of Valvular Heart Disease Based on Pathologic Examination of Valves from Patients over 14 Years of Age*

Valve Involved	Rheumatic	Non-Rheumatic
Only Aortic (163)†	13%	87%
Mitral and Aortic (116)†	97%	3%
Only Mitral (75)†	76%	24%
Mitral, Aortic, and Tricuspid (38)†	97%	3%

*Adapted from Roberts Amer J Med 49:151, 1970.
†Number in parentheses represents the number of specimens examined.

These examples strongly suggest that the incidence data which we have available for analysis today are inaccurate. We are recognizing that rheumatic fever represents a special problem among certain disadvantaged populations. Because of the tendency for the lack of comprehensive health care in some areas[13] and because of apparently inconsistent reporting of cases by physicians, underreporting of cases of rheumatic fever probably occurs. On the other hand, failure to make accurate diagnoses of valvular heart disease due to other causes—as well as the tendency to make a diagnosis of rheumatic fever despite failure to fulfill the Jones Criteria[14] leads to overreporting. While the actual incidence of rheumatic fever has probably fallen in the last three decades in the United States, presently available data are not helpful in understanding all of the reasons why this has occurred.

Postulated Mechanisms in the Pathogenesis of Rheumatic Fever

Numerous attempts have been made to define the still elusive pathogenetic mechanisms responsible for the development of rheumatic fever and rheumatic heart disease. Figure 1 illustrates three of the most frequently discussed concepts of pathogenetic mechanisms responsible for the development of rheumatic fever.

Infection of Heart Valves with Group A Streptococci

Group A streptococcal infection of heart valves has been considered to be a likely explanation for

rheumatic fever (Figure 1A). Almost 25 years ago three groups of investigators independently reported that they were able to grow hemolytic streptococci from heart valves affected by rheumatic valvulitis in a large percentage of patients dying from acute rheumatic fever.[15-17] In 1961, however, Watson and colleagues, using very careful culture techniques in 11 patients dying with acute rheumatic fever, were essentially unable to isolate the organism from affected valves.[18] This latter study has satisfied most investigators that acute rheumatic fever is not due to direct streptococcal infection of the valves. Wittler and coworkers have raised the possibility that bacterial L-forms are involved in the pathogenesis of rheumatic valvulitis,[19] but this has not been substantiated.

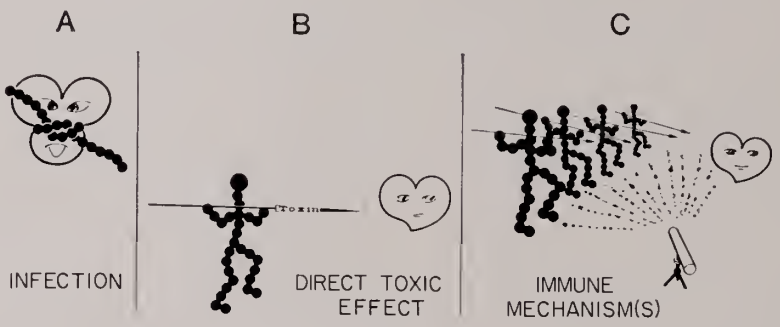


Figure 1

Toxic Effect of Streptococcal Products

A second possible explanation (Figure 1B) recognizes that some somatic components of the group A streptococcus as well as several of the extracellular products of this organism are toxic for animal tissues. The theory postulates that these "toxins" are responsible for the development of rheumatic fever by directly affecting the heart and other tissues.

Several components of the streptococcal cell wall have been studied in this regard. For example, *M protein,* the virulence factor of the group A streptococcus, has been considered to be a likely candidate. This material, under specific experimental conditions, can result in toxic effects on animal tissues.[20] The *group specific polysaccharide,* a component of the streptococcal cell wall which determines the group (A, B, C, G, etc.) of beta hemolytic streptococci, is generally felt to be non-toxic to animals,[21] but there are data which do suggest toxicity of this substance for rabbit myocardium.[22] Although toxicity has been experimentally demonstrated for these antigens, their effects do not closely mimic either the clinical picture or the pathologic findings of rheumatic fever in the human. These observations remain interesting, but their pathogenetic significance is unknown.

Extracellular products of group A streptococci which have been considered in the "toxic hypotheses" include the hemolysins, *streptolysin S* and *streptolysin O.* Streptolysin S is not antigenic. When injected into the knee joints of rabbits, it causes chronic arthritis.[23,24] It has been suggested that patients with rheumatic fever are unable to neutralize streptolysin S.[25] If it is not antigenic, it might remain "free" in the body and result in tissue damage. However, data to incriminate streptolysin S in the pathogenesis of rheumatic fever are not available.

Streptolysin O is a very potent oxygen labile hemolysin; in fact, it can be lethal. It has direct cardiotoxic actions.[26] The myocardial toxicity of streptolysin O can be easily demonstrated. In Figure 2—on the left—are myocardial cells from a seven day chicken embryo growing in tissue culture. After being exposed to a minute amount of streptolysin O for only five minutes it can be seen that the cell rapidly disintegrates (Figure 2, right). Ginsburg has speculated that the role of streptolysin O in the pathogenesis of rheumatic fever may be related either to a direct toxic action on the myocardium or to an effect on the myocardium which might then induce an immunologic reaction causing further myocardial damage.[27]

Autoimmunity

The third and perhaps the most intriguing theory of the pathogenesis of rheumatic fever is illustrated by Figure 1C. The hypothesis acknowl-

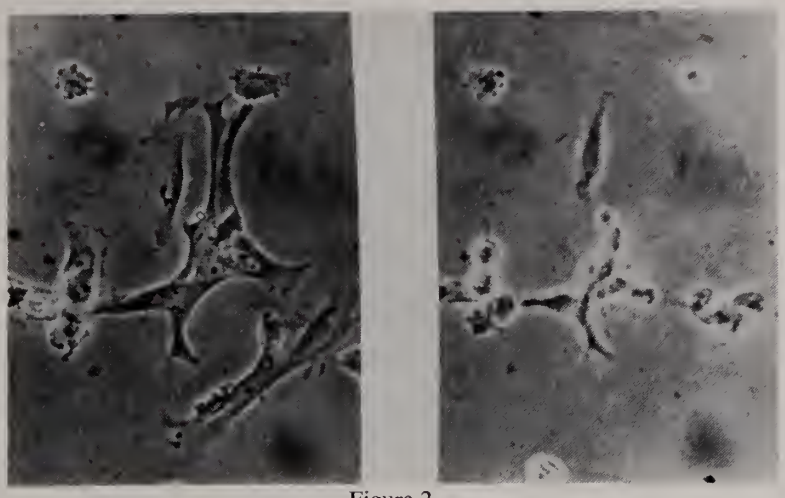


Figure 2

edges the similarity of certain components of the streptococcal cell and components of human myocardium or valvular tissue. The theory suggests that at the time of a streptococcal infection the host immune defenses recognize the foreign streptococcal antigen(s), leading to specific antibody production. Because of the antigenic similarity, these antibodies "attack" the host as well as the organism and cause cardiac damage.

Evidence to support an antigenic relationship ("cross-reactive antigens") between human heart and streptococcal cellular antigens basically falls into two categories. One involves a relationship between the sarcolemma (the cell membrane of the myocardial cell) and portions of the streptococcal cell membrane and/or the streptococcal cell wall. The second involves a similarity between the glycoprotein in heart valves and the group A polysaccharide moiety of the streptococcal cell wall.

In the early 1960's Dr. Melvin Kaplan and his colleagues demonstrated that anti-sera to partially purified cell wall components of selected types of group A streptococci reacted with human myocardium as well as skeletal muscle, smooth muscle, vessel walls, and endocardium.[28-30] A few years later, Zabriskie and Freimer described an antigenic relationship between the myocardial sarcolemma and somatic antigens of the streptococcal cell, but these investigators felt that the cell membrane contained the "cross reactive" antigen.[31] Studies have shown that the sera of 20 to 80 percent of patients with acute rheumatic fever contain these "heart reactive antibodies," antibodies in sera which react with myocardium.[32,33] While these antibodies can be demonstrated in sera of a large percentage of patients with rheumatic fever, they are also present in sera of some patients with uncomplicated streptococcal infection.[33] The significance of these findings is not fully understood.

Dudding and Ayoub found prolonged persistence of antibody to the group A carbohydrate in sera of patients with rheumatic valvular heart disease when compared with sera of patients with uncomplicated streptococcal pharyngitis, Sydenham's chorea, or acute post-streptococcal glomerulonephritis.[34] However, studies by Zimmerman, et al, using a different technique for measuring anti-A carbohydrate antibody, were not able to confirm the persistence of this antibody in patients with rheumatic valvular heart disease.[35] Nonetheless, subsequent studies lent support to the original hypothesis by demonstrating that, in patients with rheumatic valvular heart disease undergoing replacement of the diseased valve, levels of antibody to the group A carbohydrate fell following surgery, certainly a fascinating observation as it would suggest removal of the antigenic stimulus for group A carbohydrate antibody production.[36] Furthermore this antibody was not found to be present in sera of patients with bacterial endocarditis, a nonspecific "valvulitis"[37] or in patients with congenital mitral valve disease.[39]

Whether one is attracted to either the "cross-reaction" between the myocardium and the streptococcal cell wall or cell membrane antigen, or to the similarity involving heart valves and the streptococcal group specific polysaccharide these theories are intriguing and deserve additional evaluation. Important unanswered questions remain. While there is a temporal relationship between the presence of so-called "heart reactive

antibodies" and the onset and clinical activity of rheumatic fever, the pathogenetic mechanisms are unknown. The question has been raised as to whether these antibodies represent the "horse or the cart." Is antibody formation due to cardiac damage from some as yet unknown substance, or does cardiac damage result from production of these antibodies?

Tagg and McGiven, noting a lack of toxicity of human sera containing "heart reactive antibodies" for mammalian heart cells, have suggested that these antibodies are formed as a part of an immunological response to heart tissue damaged by some other agent. These investigators showed that streptocin A, a bacterocin produced by group A streptococci, is toxic for myocytes and hypothesized that this material might modify cardiac antigens and/or release cytoplasmic cardiac antigens which subsequently evoke an immune response and lead to carditis.[39]

There are also puzzling questions about the group A carbohydrate antibody. For example, it is apparent in patients as well as in experimental animals, that antibodies to the group A carbohydrate develop following skin infection, just as they do following streptococcal pharyngitis,[40-42] yet rheumatic fever does not occur following pyoderma.[43] How can this fact be compatible with this theory? Furthermore, from embryologic studies it is known that heart valves are formed from a common "source" and yet if we are to incriminate the group A carbohydrate antibody in the pathogenesis of rheumatic fever we must ask why left heart valves are affected more frequently than are the tricuspid and pulmonary valves?

Other Possible Pathogenetic Mechanisms

There are several other concepts of the pathogenesis of rheumatic fever which do not fit neatly into the three previously mentioned theories. Investigators have speculated about a possible role for viruses in the pathogenesis of "rheumatic" heart disease.[44] It has been suggested that about one-third of patients with rheumatic fever have no history of a preceding upper respiratory tract infection, i.e. strep throat.[8,45] Proponents of the viral theory would contend that the precipitating event may not be the "typical" streptococcal upper respiratory tract infection, but a viral one—perhaps even subclinical. Dr. George Burch and his collcagues have produced valvular lesions in the primate with Coxsackie viruses.[46] They also have reported the presence of viral antigens (demonstrated by fluorescent microscopy) in human valves.[47] These data might suggest viruses as a possible cause for acquired valvular heart disease. However, there is no evidence which confirms that viruses, are in fact, responsible for the clinical syndrome of rheumatic fever or the subsequent development of rheumatic heart disease.

Several attractive hypotheses to explain rheumatic fever recognize a possible influence of the site of the group A streptococcal infection. Rheumatic fever does not follow streptococcal pyoderma and Wannamaker has suggested that this may be an important clue.[43] Streptolysin O has been postulated to be involved in the pathogenesis of rheumatic fever. It is known that anti-streptolysin O titers following streptococcal pyoderma are more feeble than those following upper respiratory tract infection.[48-50] In our laboratory, we have shown in the experimental animal that lipids such as cholesterol, which are present in abundance in skin, are capable of altering the antigenicity of streptolysin O.[52] Lipids in skin might modify the antigenicity of the group A streptococcus or its products (such as streptolysin O) in such a way so that the responsible antigenic stimulus is never presented to the host and rheumatic fever does not develop. Other than the fact that the potential for this antigenic modification by lipid appears to be selective for streptolysin O,[52] there is as yet no direct evidence to link this to the pathogenesis of rheumatic fever.

The influence of the site of the preceding group A streptococcal infection has been considered in yet another way. Stollerman has suggested that, just as there are "nephritogenic" and "non-nephritogenic" group A streptococci, there may also be "rheumatogenic" and "non-rheumatogenic" streptococci. Noting that there are certain serological types of group A streptococci (so called "skin strains") which infrequently cause upper respiratory tract infection (and even when they do, don't appear associated with the development of rheumatic fever), he has suggested that it may be an as yet undefined component or product of certain strains of group A streptococci which are often responsible for pharyngitis and the development of rheumatic fever which makes them "rheumatogenic."[53]

The pathogenetic mechanism(s) responsible for the development of acute rheumatic fever remain an enigma. During the last three decades

significant and important contributions have been made by clinicians, epidemiologists, and basic scientists toward solving the riddle of this disease which, in some parts of the world, is responsible for so much of the morbidity and mortality due to cardiac disease. Once the puzzle has been solved and the mechanisms for producing this unusual disease are fully understood, additional and perhaps more efficient methods of prevention may become available. Until that time, prevention of this non-suppurative sequelae of streptococcal infection requires control of the precipitating infections.

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Acute Post-Streptococcal Glomerulonephritis and Its Relationship to the Epidemiology of Streptococcal Infections

PATRICIA FERRIERI, M.D.*

Acute post-streptococcal glomerulonephritis may follow streptococcal infections of the throat or skin. Clinical, epidemiological, microbiologic and immunologic features of nephritis following infection at either site are presented in this paper.

THE EMPHASIS IN discussions of community control of streptococcal infections and their sequelae has ordinarily been on respiratory tract infections. During the past several years investigations of the epidemiology of streptococcal skin disease have led to a resurgence of interest in the skin as a site of infection.

For the purposes of this presentation, acute glomerulonephritis, a non-suppurative sequela of group A streptococcal infections of either the throat or the skin, will be discussed with particular emphasis on features of streptococcal skin disease. Although acute nephritis has been reported on occasion following infection with other agents, convincing data to rule out a streptococcal etiology has frequently been lacking. There are abundant epidemiological, clinical, microbiologic and immunologic data to support the group A streptococcus as the leading agent of infection preceding acute glomerulonephritis.[1-8]

Clinical Considerations

Clinical findings of acute glomerulonephritis (AGN) which may be seen on presentation to a hospital or physician include hematuria, edema, decreased urine output, fever, hypertension, and congestive heart failure. Usually more than one of these findings is present, but at times the disease is very mild and hematuria may be obvious only by microscopic examination.

Epidemiologic studies have revealed a wide spectrum of clinical severity, and clearly, patients with mild or subclinical disease may not come to medical attention. Laboratory findings can include red cell casts and proteinuria in addition to hematuria and elevations of sedimentation rate. Evidence of renal function impairment includes elevations of urea nitrogen, creatinine, and serum potassium. Depression of serum complement levels, either total hemolytic complement or β1C, can be helpful as an indication of the immunological process going on with deposition of complement (β1C) and gamma globulin (not invariable) in the glomeruli.

Elevated streptococcal antibody titers or evidence of a rise or fall in titers on sequential occasions can be valuable in documenting the previous streptococcal infection. Not uncommonly one may not isolate the streptococcus from throat cultures, and in the case of skin disease, the lesions may have healed before evidence of renal disease was manifest. In past years scarlet fever not uncommonly preceded appearance of nephritis.

Epidemiological Considerations

Epidemiologic differences exist between pharyngitis-associated nephritis and impetigo or pyoderma-associated nephritis. Similarities exist in the clinical and pathological findings, but differences are seen in the age distribution following infection in the throat vs. skin. Generally the peak incidence of pyoderma-associated nephritis is under six years of age, whereas pharyngitis-associated nephritis is

*Associate Professor, Department of Pediatrics, University of Minnesota Medical School, Minneapolis, Minnesota.

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a disease of school-age children.[1-2] A 2:1 predominance of males to females has been reported in nephritis following pharyngitis;[3] in contrast an equal sex distribution has been reported following skin infections.[4,5] The latency period is shorter (10 days)[2] in AGN following pharyngitis compared to pyoderma (18-21 days or longer).[4]

It is unclear why there is a longer latency period for acute nephritis following skin infections compared with nephritis following throat infections. The attack rates (10-15%) may be quite variable but similar.[6] Multiple cases may occur in families following both types of infection. The group A streptococcal serotypes with nephritogenic potential are limited, but there is a distinct difference between the serotypes associated with pharyngitis-associated AGN vs. pyoderma-associated AGN and these will be discussed in more detail. The immune response to streptococcal antigens is good in AGN following pharyngitis, but the response following pyoderma is variable, the anti-DNase B response being of particular value.[6] There is a marked winter and spring incidence of pharyngitis-associated AGN, paralleling the peaks of streptococcal respiratory infection, but the peak incidence of pyoderma-associated AGN is late summer and early fall, a time of peak frequency of impetigo. However, in tropical climates the distribution of pyoderma-associated AGN is frequently year-round. Both diseases are seen in both the northern and southern United States, and indeed are of world-wide distribution.[6,7]

The concept of the nephritogenic potential of certain streptococcal types, particularly that of M-type 12, was pioneered by Dr. Rammelkamp and his associates and was then confirmed from other parts of the world.[8] He pointed out that differences in attack rates of acute nephritis following streptococcal infections appear to be due to varying nephritogenic capacities of the infecting organism, and that some strains of type 12 may vary in their nephritogenic capacity.[2,8]

A comparison of streptococcal serotypes associated with nephritis following pharyngitis vs. disease following skin infections reveals several differences as shown in Table 1. M-type 12 is the predominant strain associated with acute nephritis following pharyngitis or tonsillitis.[2] There is also good evidence that infections of the upper respiratory tract due to types 1 and 4 may result in AGN, and reasonable evidence for types 3, 25, and 49.[6,9] Several pyoderma strains have been associated with outbreaks of nephritis, notably M-type 49, frequently referred to as the Red Lake strain. This type has also been associated with nephritis following infection of the upper respiratory tract.[1] There is strong or good evidence of association of types 2 (T-pattern 8/25/Imp. 19), 55, 57, and 60 with pyoderma nephritis.[9-12] Reasonable evidence also exists for the association of types 52 and 59 and to a less extent of 31, 56 and 61 with nephritis.[9] It can be seen that many of these strains associated with pyoderma nephritis are higher numbered types which are intriguing, which appear to have a predilection for infecting the skin, and when isolated from the upper respiratory tract may be thought of as secondary contaminants ordinarily, as will be described later.

Many epidemics of nephritis have been reported

TABLE I
Streptococcal Serotypes Associated with Acute Nephritis

Serotype		Acute Nephritis	Acute Nephritis
M-Type	T-Pattern	Following Pharyngitis	Following Pyoderma
1	1	+++*	±
2	8/25/Imp. 19	0	+++
3	3/13/B	++	±
4	4	+++	±
12	12	++++	±
25	8/25/Imp. 19	++	±
31	—	0	+
49	14/49	++	++++
52	3/13/B	0	++
55	8/25/Imp. 19	0	++++
56	28	0	+
57	8/25/Imp. 19	0	++++
59	5/11/12/27/44	0	++
60	4	0	+++
61	5/11/12/27/44	0	+

*Strength of association designated as follows: ++++ excellent evidence of association; +++ good evidence; ++ reasonably good; + limited evidence; ± or 0 questionable or no association with nephritis.

from the United States and other parts of the world in association with disease due to some of these streptococcal serotypes. A large outbreak of acute nephritis following respiratory infections due to type 12 occurred at the United States Naval Station at Bainbridge, Maryland in 1951-1952.[2] Examples of nephritis following skin infections include large-scale epidemics in Trinidad associated with streptococcal pyoderma due to types 55, 49, and 57, as well as, an outbreak in Israel associated with M-type 55.[10,12] Not uncommonly, new strains will emerge at intervals in a population and after a period of years may reappear and be responsible for a new outbreak of nephritis due to the same type—e.g. the M-49 epidemic of nephritis in 1953 and again in 1966 at Red Lake, Minnesota.[4] M-type 49 is also known to have a world-wide distribution.[13]

Before considering other epidemiological features of streptococcal infections it may be appropriate to briefly describe the appearance of streptococcal impetigo in various stages of development since this may be less common knowledge than the appearance of the pharynx in streptococcal upper respiratory tract infections. An early lesion is the vesicle with (minimal or no erythema) which ordinarily yields beta hemolytic streptococci in pure culture. This stage ordinarily persists for less than 24 hours and then one sees the progression to pustular and then crusted and pustular skin lesions, which commonly yield both streptococci and coagulase-positive staphylococci. The crusts of these lesions are thick, amber in color and crumble; this is in contrast to pure staphylococcal lesions which may have thin, varnish-like, light brown crusts or appear as bullous lesions.

Not uncommonly other skin conditions may be associated with streptococcal pyoderma. These include abrasions, wounds, burns, mosquito-bites, chronic eczema, dermatitis venenata, scabies, varicella and pediculosis. These conditions of the skin, with the implication of trauma, may precede or accompany streptococcal skin disease.

Epidemiologic studies have permitted an understanding of the appearance and sequential spread of group A streptococci among different body sites and the relationship of these events to the development of impetigo.[14] A concept which emerged from these studies is depicted in Figure 1. Group A streptococci, from uncertain sources, are deposited on or possibly colonize the normal skin.

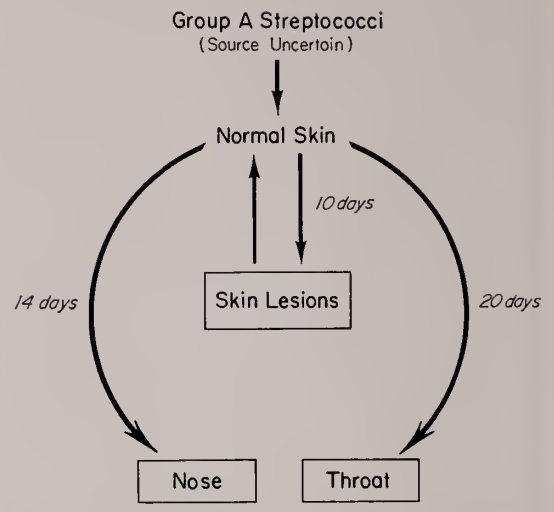


Fig. 1—Concept of the sequence of spread of group A streptococci among different body sites. (Reproduced with modification from Ferrieri et al.: J Clin Invest 51: 2851-2862, 1972.) (Permission granted.)

After such insults as insect bites, abrasions, or even undetectable trauma, skin lesions due to the same serological type may appear after a mean interval of 10 days if streptococci are present on the normal skin.

Respiratory tract acquisition of streptococci ordinarily follows skin acquisition of streptococci with mean intervals of 14 days for the nose and 20 days for the throat, and usually does not occur until after the development of skin lesions, suggesting transmission from normal or infected skin sites. This respiratory tract acquisition of organisms was frequently transitory and clinical evidence of streptococcal respiratory disease was not seen.

If one examines, on the basis of these studies, the distribution of positive streptococcal cultures

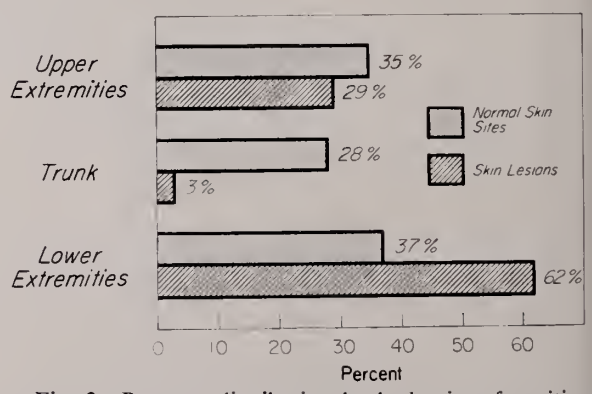


Fig. 2—Per cent distribution by body site of positive cultures for group A streptococci from normal skin and from skin lesions. (Reproduced from Ferrieri et al.: J Clin Invest 51:2851-2862, 1972.) (Permission granted.)

from normal skin compared to skin lesions one sees that the percentage distribution of positive normal skin sites was similar among the upper and lower extremities and trunk (back)—ranging from 28 to 37%—whereas the lower extremities accounted for 62% of the total lesions harboring group A streptococci (Figure 2). It is clear that less exposed parts of the body (i.e. the back) can acquire the organisms, but since the majority of lesions were on the legs, such factors as trauma may be etiologically important in the development of skin lesions in a setting where the organisms are available to invade the skin.

In this same population of children there was a higher frequency of pyoderma in children two to five years of age compared to older children. There was no significant difference in distribution by sex. It has been our clinical impression over the years that older children tend to have less severe and fewer numbers of skin lesions.

Of interest has been the spread of group A streptococci within family units which bears on the common finding that multiple cases of nephritis can occur following introduction of a nephritogenic strain into a family. Intervals from the first recovery of organisms from the normal skin and/or lesions to the time of secondary acquisition have been compared with data on acquisition of streptococci in the throat of family members under prolonged observation in the Cleveland study done several years ago. The short interval of 4.8 days for secondary family spread of pyoderma streptococci[14] contrasts with 15 days observed between index and secondary acquisition of streptococci in the throat.

Studies of differences in frequency of nephritis following M-type 49 infections at different sites reveal a higher frequency of AGN after skin infection than after infection of the throat (11.9% vs. 2.3%).[1] Simultaneous infection did not significantly alter the attack rate. These observations support the primary role of the skin as a site of infection preceding nephritis associated with pyoderma strains of streptococci and suggest that the capacity for such pyoderma strains to cause infection of the throat may be more limited.

Variations in the immune response to streptococcal antigens in patients with nephritis were alluded to earlier. Table 2 demonstrates in a semi-quantitative fashion responses to streptococcal extracellular antigens—e.g. deoxyribonuclease B (DNase B), streptolysin O, nicotinamide adenine dinucleotidase (NADase), and hyaluronidase in patients with nephritis following pharyngitis and pyoderma. Among the four indicated streptococcal antibody tests, there is a good to excellent response in all patients with nephritis after throat infections and some superiority of the anti-DNase B or anti-hyaluronidase test in patients with pyoderma nephritis.[6,15,16] The poorer response in the latter condition to streptolysin O may be a reflection of poor antigenicity following skin sites of infection, a finding being pursued in animal studies by Kaplan and Wannamaker.[17] These findings summarized here tend to parallel (but are more marked) the immune responses following infection at these two sites in patients without nephritis.

Prevention of Streptococcal Infections

Approaches to control streptococcal infections have concentrated primarily on the prophylaxis of streptococcal pharyngitis and several studies in military populations are available in the literature.[18,19] Programs for the detection of streptococcal respiratory carriage in school children and early treatment of pharyngitis are in effect in many parts of the country under the direction of health departments.

In a pilot study, we attempted mass prophylaxis of streptococcal skin disease in 1971 in 78 children from 18 families with a history of past experience with impetigo.[20,21] By a double-blind cross-over design long-acting benzathine penicillin or a saline placebo was given, followed six weeks later by the opposite of the first injection. A smaller group of children received no injections because of a history of penicillin allergy. Figure 3 reveals a comparison of prevalence of skin lesions in the three groups.[21] In the "no injection"

TABLE 2
Responses to Streptococcal Antigens as Measured by Antibody Tests*

Acute Nephritis	Anti-DNase B	ASO	Anti-NADase	Anti-hyaluronidase
Following pharyngitis	+++	+++	++++	+++
Following Pyoderma	++++	++	++	++++

*++++ indicates excellent response; +++ good response; ++ some response.

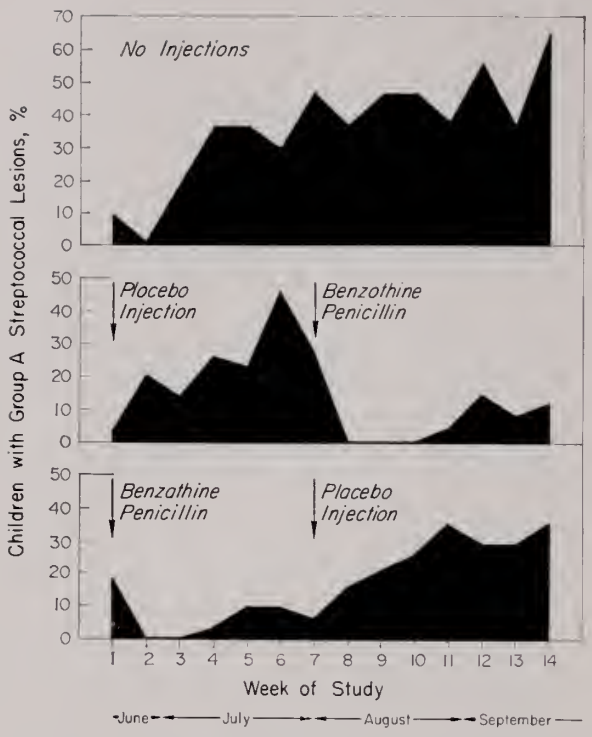


Fig. 3—Percentage of children in each of the 3 groups with skin lesions positive for group A streptococci for each week of the study. Arrows indicate when benzathine penicillin or placebo was given. (Reproduced from Ferrieri et al.: Excerpta Medica, Amsterdam, 1974, p. 258-265.) (Permission granted.)

group lesions were common throughout the study. A lower frequency of lesions was seen in the other two groups during the periods after penicillin injection with a steady increase in lesions during the periods after placebo injection.

The prevalence of skin lesions at weekly intervals following penicillin and placebo injections is seen in Table 3. There was a two-week period without lesions following penicillin and then a progressive rise in the frequency through the fifth week. Prevalence rates were highest five weeks after the injections. The mean prevalence rates were significantly lower after penicillin than after placebo.

This approach afforded a beneficial influence on decreasing skin lesions in children at risk for developing streptococcal skin infections and may be useful in designing programs in populations with a high frequency of disease. For continuous control repeated injections would probably be required and in the absence of a threat of a nephritogenic strain moving into a population, such a massive effort with its limitations and possible hazards may be unwarranted.

Prevention of acute glomerulonephritis is a more difficult undertaking. Acute nephritis following streptococcal pharyngitis due to epidemic nephritogenic strains may be partially preventable ($\cong 50\%$) by treatment of the infection.[2,6] Whether penicillin treatment of streptococcal skin infections will reduce the frequency of nephritis is less clear, and no controlled studies to date are available to answer the question.

References will be found on page 615.

Acknowledgments

Figure 1 is modified from and Figure 2 reproduced from a previous publication[14] and with permission from the Rockefeller University Press.

Figure 3 is reproduced from a previous report[21] and with permission from EXCERPTA MEDICA.

Table 3 is modified from a previous publication[20] and with permission from the University of Chicago Press.

TABLE 3
Prevalence of Skin Lesions in Children by Week Following Benzathine Penicillin and Placebo Injections

	Benzathine Penicillin		Placebo	
Interval after Injection (Weeks)	No. with Lesions/ No. Seen*	Prevalence rate (%)†	No. with Lesions/ No. Seen	Prevalence rate (%)†
1	0/59	0	11/61	18.0
2	0/59	0	12/61	19.7
3	1/61	1.6	17/61	27.9
4	5/55	9.1	18/63	28.6
5	8/57	14.0	23/55	41.8
6	5/54	9.3	18/57	31.6

*No. children seen represents the combined number whether the injection (either benzathine penicillin or placebo) was given at the first or the second injection date.
†The mean prevalence rate during the 6 week period was 6% following benzathine penicillin and 28% following placebo. This observed difference is significant: >3 times the standard error.
(Modified from Ferrieri et al.: J Infect Dis, 129:429, 1974. ©1974 by the University of Chicago.)
(Permission granted.)

Control of Streptococcal Infections

Principles and Problems

MILTON MARKOWITZ, M.D.*

Streptococcal infections are still frequent despite the availablility of effective antimicrobials for more than two decades. The reasons for our failure to eradicate these infections are discussed.

SOCIAL AND SCIENTIFIC progress has brought about the near extinction of several infectious diseases, e.g., typhoid fever and diphtheria. Still other conditions, such as poliomyelitis and measles, are nearly under control or at least there is the capacity to control them.

In contrast to these advances, streptococcal infections have neither been eradicated nor even very well controlled. This is not to suggest that the streptococcus has been untouched by progress. There has been a marked decline in the death rate from scarlet fever.[1] This decline occurred before antimicrobial drugs became available and therefore was due to factors other than scientific advances. Not only are streptococcal infections generally milder, but epidemics are less frequent, and suppurative complications have become much less common than in the past.

When antibiotics became available and when these drugs proved to be strikingly effective against streptococcal infections, few would have predicted the need to conduct conferences such as this more than a generation later. In fact, pharyngeal and skin streptococcal infections are probably still the most common bacterial infections in children. Acute glomerulonephritis and rheumatic fever continue to occur and we still see occasional patients with severe streptococcal sepsis.

The purpose of this paper is to briefly review: (1) the role of environmental factors in the control of streptococcal infections, (2) attempts to alter host susceptibility and (3) methods to reduce streptococcal carriage.

Environmental Factors

Environmental factors are of great importance in spreading all infectious diseases. Changing the environment has brought many of these infections under control. For example, improving sanitation, providing pure water, and reducing the rat population greatly influenced the incidence of typhoid fever, cholera and the plague. However, in dealing with streptococcal infections, the problem is much more difficult because man is the reservoir for the infectious agent and transmission occurs from person to person.

Furthermore, many susceptible individuals are always available to support the chain of transmission indefinitely because natural immunity is type-specific and the large number of serotypes makes it virtually impossible to develop total immunity to these organisms. Spread occurs via large droplets during fairly close contact; hence, crowding is an important environmental factor. A number of studies have shown that where crowding exists, whether in army barracks, in inadequately housed families or in schools, the spread of streptococcal infections is enhanced.

We have already noted the marked decline in mortality from scarlet fever. The falling mortality is probably associated with improved social conditions. There has also been a change in the epidemiologic spectrum of streptococcal infections so that illnesses due to these bacteria are generally milder. Individuals with few symptoms and subclinical infections go about their daily business and are much more likely to transmit the orga-

*Department of Pediatrics, University of Connecticut School of Medicine, Hartford, Connecticut.

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nism to others. In our urbanized society, there is ample opportunity for spreading infections, especially for the children who live in crowded, substandard neighborhoods.

There are no good data on the incidence of streptococcal infections. In an effort to estimate present day children's experience with streptococcal infections, Doctor Quinn studied the Dick Test reaction in different groups of Nashville school children.[2] He found that more than twice as many children from inner city schools were Dick Test negative (immune to scarlet fever toxin) when compared to children from middle class schools.

These results are not surprising. What is surprising was that the data differed little from that obtained from similar studies carried out 45 years previously in New York City.[3] These findings suggest that the frequency of streptococcal infections among certain populations has not changed much. This is also true for the complications of streptococcal infections. In the Baltimore studies, most cases of rheumatic fever were clustered in the low income areas and furthermore, that the incidence of *first* attacks was not much lower than in the 1930's.[4]

As many previous studies have shown, the Baltimore data showed a close relationship between crowding and the incidence of rheumatic fever.[5] How can one control crowding short of reversing the trend toward urbanization and abolishing poverty, neither of which is very likely?

More amenable to change than crowding is still another environmental or societal factor, namely, the accessability and adequacy of medical care. There is now fairly good evidence that the availability of good medical care can reduce the incidence of post-streptococcal complications, such as rheumatic fever, even though living conditions have not otherwise improved. Dr. Gordis studied the incidence of rheumatic fever in Baltimore's inner city census tracts before and after the establishment of special health care programs for children in these areas.[6] The programs provided extensive culturing for streptococcal infections and close attention to adequate treatment when such infections were identified. Gordis showed a significant decrease in rheumatic fever in the comprehensive care tracts as compared to the rest of the city. This study demonstrates beautifully that much can be done without waiting for the millennium to come when the socioeconomic gap between various classes will be narrowed and the crowded ghettoes disappear.

Altering Host Susceptibility

Another approach to controlling streptococcal infection is to try to alter the susceptibility of the host. One of the earliest efforts to prevent streptococcal sore throats was by tonsillectomy. This procedure is still common. About one million tonsillectomies are done each year in this country at an enormous cost and with an occasional death. The indications for this operation are vague and varied, but repeated, suspected streptococcal sore throats are cited as a common reason. Although there are conflicting opinions on this subject, the weight of evidence favors the view that removing tonsils does not significantly reduce the risk of subsequent streptococcal infections.[7] In fact, the absence of tonsils increases the chances of missing streptococcal infections of the pharynx because signs and symptoms are often less pronounced and it is more difficult to isolate streptococci from the throat.

A much more effective way to prevent streptococcal infections is by small daily doses of antimicrobial agents. This form of control has been proven beyond any doubt, but it is limited to a selected group of patients with a history of rheumatic fever or inactive rheumatic heart disease and is not applicable for the general population.

Streptococcal Vaccine

Work on a streptococcal vaccine has been going on in several laboratories for a number of years. Progress has been made in the purification of M protein, the cellular antigen involved in immunity to streptococcal infections. This material has been injected into humans and type-specific antibodies produced which appear to be protective.

The immediate reactions to the vaccine have not been a problem in individuals who have negative skin tests to the material, and in general young patients have tolerated the vaccine well. However, the possibility of delayed cytotoxic reactions has not been excluded and there is considerable concern that the vaccine may carry a risk for individuals who need the protection the most, i.e., children from rheumatic families.[8] A vaccine given by nasal spray may produce protective antibodies and may carry less risk of reactions.[9] Apart from safety however, the multi-

plicity of streptococcal types and the lack of cross-protection among these types probably precludes the development of a completely effective vaccine. Based on current knowledge, the best that can be anticipated is a multivalent vaccine against the more prevalent types and even such a vaccine is probably years away.

Reducing the Number of Dangerous Carriers

In the absence of a vaccine, the only way to reduce the incidence of streptococcal infections is by reducing the number of carriers capable of transmitting infections. This can be accomplished by identifying the dangerous carriers and treating them until the organisms are eliminated or greatly reduced in number. Dangerous carriers are individuals with clinical or subclinical infections during the acute phase and for the next two or three weeks. Streptococci can persist in the throat for much longer periods of time, but these chronic carriers usually harbor few organisms, often nontypable, and are probably not responsible for the spread of infections.

Diagnostic Precision

The problem of identifying patients with acute infections is complicated because in addition to those who are clinically ill and seek care, there are many who are symptomatic but for one reason or another do not seek medical attention. There are also those with active infections who are completely asymptomatic. Identifying infections in these latter groups among the general population will be reviewed by others and this discussion will be limited to the patients with pharyngitis who are seen by a physician.

Much has been written about the difficulties in making a diagnosis of streptococcal pharyngitis based on clinical findings and studies documenting these difficulties need not be repeated in detail. Apart from a scarletinal rash, there is no single nor any combination of findings which indicate with certainty the presence or absence of a streptococcal infection. To quote Doctor Wannamaker, "few modern thinking pediatricians attempt to make this diagnosis on the basis of clinical findings alone."[10]

There are still physicians who take exception to the recommendation that a throat culture is indicated in all patients with pharyngitis. However, a recent litigation involving a child who did not have a throat culture taken and who subsequently developed rheumatic fever, which was settled in favor of the litigant, will convincingly make the throat culture an even more accepted procedure than it now is.

This is not to suggest that the throat culture solves all the problems pertaining to diagnosis. As with any laboratory procedure, it is not 100% accurate. One major limitation is that a positive culture does not distinguish between an active infection and a chronic carrier state.[11] Although the latter is rarely dangerous to others and is not at risk for complications, the physician has no alternative but to treat every child with clinical pharyngitis and a positive throat culture. It can be argued that some children will be treated unnecessarily and indeed that is true. On the other hand, over-treatment is far more common when patients with pharyngitis are managed without the benefit of throat cultures.

When to Treat

The question of whether to treat or wait for the results of the culture is not troublesome when the results of the culture are available within 24 hours. While there are always clinical situations when therapy should be instituted, physicians who interpret their own cultures are often inclined to await the report of the culture before instituting therapy. Should treatment have been started and the culture reported as negative, medication can be discontinued and both the physician and the patient benefit. The physician will have a better idea of "what's going around," the patient will be less exposed to the risk of antibiotic reactions and the family will have learned that an accurate diagnosis of pharyngitis is not less important than for more exotic illnesses.

How to Treat

The choice of the drug for patients with clinical pharyngitis and a positive throat culture is usually not a major problem, because, except for the sulfonamides and the tetracyclines, all of the commonly used antibiotics are about equally effective against beta hemolytic streptococci. There have been many excellent drug trials carried out by practicing pediatricians who have demonstrated that good research can be performed in clinical practice. A recently published study by Lester et al.[12] compared penicillin, erythromycin and a lincomycin derivative. They found that 85-90% of their patients had negative throat cultures after a 10 day course of treatment regardless of which drug was employed. They also found that a con-

venient twice daily dose of lincomycin was as effective as four doses a day and others have shown that this is also true for penicillin and erythromycin.[13]

Neither the selection of an effective antibiotic nor the dosage used is as much a problem as maintaining treatment for a full 10 days, either because an insufficient course of treatment was prescribed or the patient stopped medication prematurely. Physicians frequently ask why a 10 day course rather than five, especially since the patient is usually clinically well in 72 hours. It is true that after five days of therapy the throat culture is negative in 98% of patients. Many years ago, Denny and co-workers showed that the culture became positive again in most patients after a five-day course of treatment.[14] Furthermore, it has been shown that the risk of developing rheumatic fever is related to the persistence of streptococci in the throat.[15]

There has been an increasing awareness of non-compliance as a significant factor in therapeutic failures. Although it is recognized that "clinic" patients frequently do not follow recommendations, studies have shown that as many as 40% of private patients do not complete a prescribed 10 day course of treatment.[16] While it is difficult to predict compliance, an effort should be made to identify factors which may lead to non-compliance. Fortunately, for the management of streptococcal infections, a single injection of benzathine penicillin is an effective alternative for patients at risk for non-compliance.

Therapeutic Failures

The reasons for bacteriologic failures in patients who complete a full course of therapy are not entirely clear. In patients with a low colony count initially it may be difficult to eradicate the organisms because it is likely they were chronic carriers from the outset. Post-treatment cultures may be limited to non-group A strains which were present prior to treatment but overgrown by group A strains. Re-acquisition from family contacts can occur but does not account for most cases with post-treatment positive cultures. A small percentage of patients acquire a new type and are not really treatment failures. Persistence of L-forms has been suspected but never proven. Although it is easier to culture streptococci from patients with tonsils, it has not been possible to correlate bacteriologic failures with the presence or absence of tonsils. Finally, there is no evidence that penicillinase-producing staphylococci in the pharynx interfere with the action of penicillin.

How should patients with a positive culture after a prescribed course of treatment be managed? A second course of therapy is indicated and since non-compliance cannot usually be excluded as a factor, an injection of benzathine penicillin is the treatment of choice. A very small number will continue to harbor streptococci after the second course and remain chronic carriers for many weeks or months. As noted previously, these individuals usually carry small numbers of non-typable organisms and probably are not hazardous to others. Also, since they are very unlikely to develop post-streptococcal complications four to five weeks after the original infection therefore, no additional therapy is recommended. Should they become clinically ill during this period, it is usually due to an infection with a different serotype and another full course of treatment is necessary.

Because the home is an important locus for the spread of streptococci, subclinical infections should be sought for in children in the family. In large families, especially where crowded conditions exist, 40 to 50% of the children will have a positive culture within 48 hours after the index case has been identified. Physicians who process cultures in their own office and who keep the cost at a minimum, find that many families willingly participate in such a preventive health program. Other approaches to detecting subclinical infections in school populations will be discussed by other participants in this conference.

Conclusion

It is not yet possible to eradicate streptococcal infections. It is our conviction that a more concerted effort should be made to achieve the highest degree of control compatible with existing knowledge and conditions.

References will be found on page 615.

Streptococcal Control in School Children

Is It Worthwhile?

BRENDAN P. PHIBBS, M.D.*

Programs for control of streptococcal diseases and their sequelae have been organized among schoolchildren in Wyoming, Colorado, Alaska, and among Indian tribes in Arizona. Data from these studies show beyond question that organized culturing and treatment programs can reduce streptococcal isolation rates and levels of streptococcal infection consistently; data now emerging suggest that these programs are also effective in preventing rheumatic fever. Such programs are only justified in high-risk populations where adequate surveillance measures can be instituted.

RHEUMATIC FEVER IN a temperate zone population is chiefly a disease of the fall, winter and spring months and the majority of its victims are between 5 and 15 years of age.[1]

Theoretically, rheumatic fever could be eradicated if every case of streptococcal pharyngitis were diagnosed accurately and treated accurately. Several obstacles prevent attainment of this goal.

1. In practical terms definitive diagnosis of streptococcal pharyngitis is not feasible, since it can only be established by detection of rising antistreptococcal antibody titers on repeated examinations.

A presumptive diagnosis can be made when signs or symptoms of pharyngitis are accompanied by a positive culture for Group A beta hemolytic streptococci.

2. Streptococcal pharyngitis preceding rheumatic fever may frequently be asymptomatic. The studies of Czoniczer[2] and Gordis,[3] among others, have left no question that many—possibly most—of the streptococcal pharyngitides preceding documented rheumatic fever are clinically "silent."

3. The public generally (particularly in lower socioeconomic and educational strata) does not regard a sore throat as a reason for a visit to a physician.

4. Many physicians do not use cultures to establish diagnosis.

5. Some physicians do not recommend or administer adequate therapy for streptococcal pharyngitis.

To circumvent these problems a program for prevention of rheumatic fever was organized in schools in Natrona County, a traditionally heavy endemic region of central Wyoming. The goals of the program were an aggressive and continuing search for streptococcal pharyngitis throughout the school population and adequate treatment whenever the diagnosis was made.

The protocol is simple, but by no means easy to implement.[4] In every school room, every morning, the teacher asks which students have a sore throat or cold. All children admitting symptoms are sent to a central school station where throat cultures are taken. To find children with minimal or no symptoms each child is inspected once a week for pharyngeal inflammation. Those with any signs are cultured.

Fluorescent antibody identification reports are phoned from the laboratory to each school. Children with positive cultures are sent home with a form describing the nature of the infection: the form also states that treatment must be instituted, or a negative culture demonstrated, before the child can return to school. (This enforced treatment or exclusion is a unique feature of the Wyoming program, but it can, in fact, be implemented in any state in the Union, since school health and state health codes describe streptococcal pharyngitis as a communicable disease.)

This kind of program required much education of teachers, parents and physicians throughout the community.

Several thousand volunteers were trained to function as paramedical personnel to inspect and swab throats. Proper swabbing technique is cru-

*Department of Medicine, University of Arizona, Arizona Medical Center, Tucson, Arizona.

Presented at the Symposium on Community Control of Streptococcal Infections held in Minneapolis, Minnesota, June, 1974.

cial and it is the impression of the author that it may be carried on more effectively by highly trained and motivated volunteers than the average physician or nurse without special interest in streptococcal disease. The importance of reaching the lower posterior nasopharynx by raising the uvula and inducing vigorous gagging while the swab is manipulated in the nasopharynx is emphasized (Figure 1).

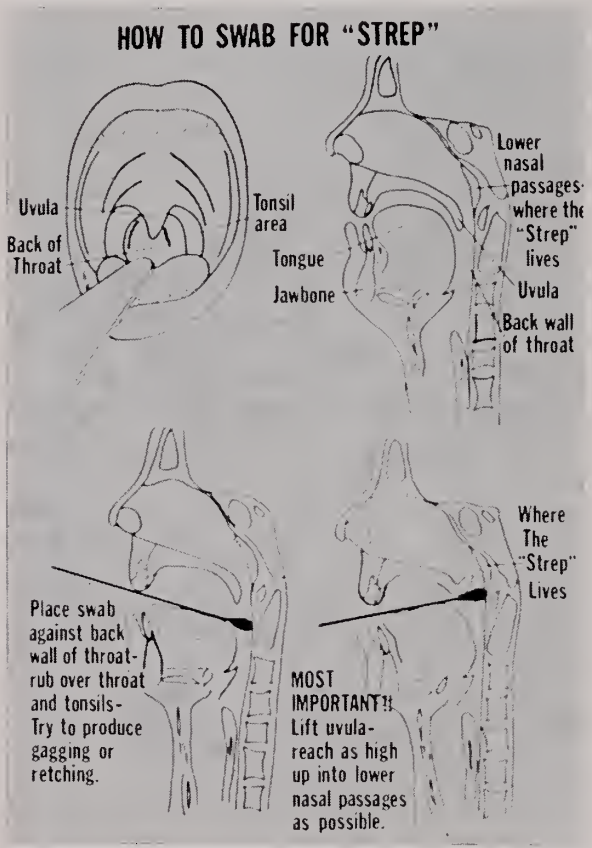


Fig 1—Diagram illustrating proper method of reaching posterior nasopharynx for maximal yield in throat swabbing for streptococci.

The program was evaluated by two ways: (1) effect on incidence of streptococcal infection and (2) effect on incidents of new cases of rheumatic fever.

Effects on Streptococcal Infection

A consistant finding of the Natrona County program was a fall in isolation rates for streptococci from 10-20% at the beginning of each school year to well below 5% before the end of the year (Figure 2).

A controlled prospective assessment of the effect of the Natrona County protocol on the streptococcal milieu was made possible by the studies of the

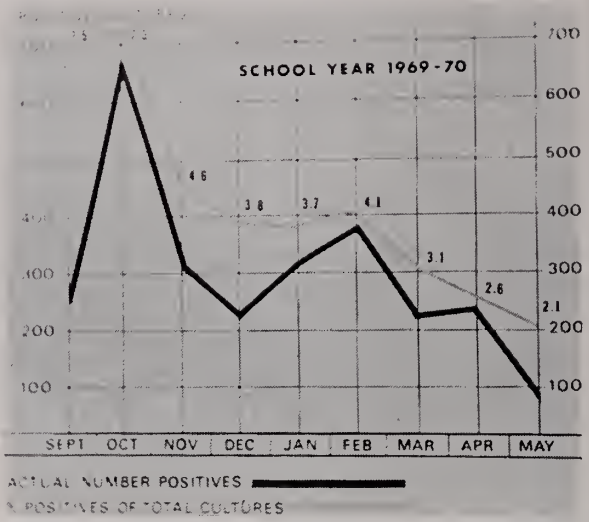


Fig. 2—Isolation rates for Group A betahemolytic streptococci among approximately 14,000 Natrona County school children in a typical year (1969-1970).

Streptococcal Section, Ecological Investigations Division, United States Public Health Service, Communicable Disease Center, Fort Collins Laboratory, under the direction of Dr. Robert Zimmerman. By fortunate coincidence, this group has been studying streptococcal epidemiology and prevalence rates in Colorado communities for 10 years. These studies provided an excellent baseline to assess the effect of the surveillance and treatment program in Wyoming. The CDC team visited Natrona County and cultured a randomized sample of 500 school children. Blood samples were drawn on all children cultured to determine levels of streptococcal antibodies.

Isolation rates in the three control Colorado communities ranged from 12-22%. The isolation

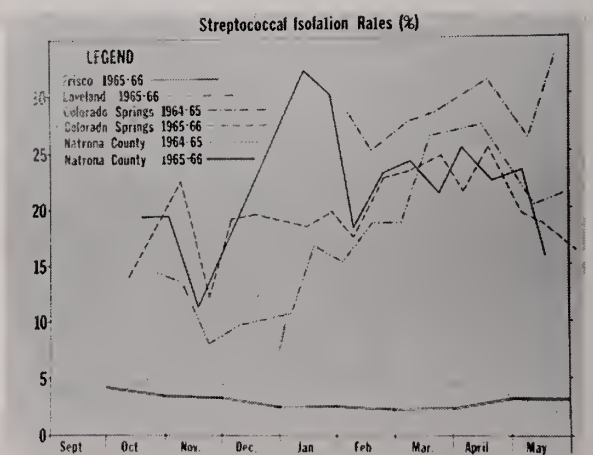


Fig. 3—Longitudinal comparison of streptococcal isolation rates in uncontrolled school child populations in three Colorado communities and in controlled school child population in Natrona County, Wyoming.

rate in the Natrona County school children (at the same time) was 1.3%—an unprecedentedly low figure for a temperate population.

Longitudinal comparison of the two populations (Figure 3) demonstrated a sustained difference in isolation rate throughout two years of comparative study.

Studies for type and group specific antistreptococcal antibodies demonstrated that the Natrona County school children had had a significantly lower rate of streptococcal exposure than their counterparts in Colorado.

Application of a similar protocol in the high-risk school population of the Sangre de Cristo School District of Southern Colorado demonstrated similar results.[6]

Zimmerman and his coworkers reproduced these results again in a controlled study in Alaskan native villages in which streptococcal disease had become epidemic. Streptococcal isolation rates in the villages under surveillance and treatment programs fell well below 5% while rates in the uncontrolled populations ranged from 20-40%.[7]

Preliminary data from school programs in the Chicago ghetto area indicate reduction of streptococcal isolation rates in difficult circumstances.[8]

In Bureau of Indian Affairs boarding schools in both Papago and Navajo areas of Arizona streptococcal disease has been recurrently epidemic: high endemic levels have been noted among day school Indian children. A Wyoming type of streptococcal control program, implemented among these children, has produced an encouraging drop in streptococcal isolation rates.[9]

Prevention of Rheumatic Fever

In Natrona County during the years 1956-7 and 1957-8, a streptococcal epidemic appeared and persisted. A large number of cases of rheumatic fever were diagnosed. At that time in the development of the Natrona County program only the school children were included: the remainder of the population can be termed a "control" group.

Figure 4 illustrates the number of cases among the school children compared to the number of cases among the uncontrolled population in the county. School children should normally have about 80% of new cases of rheumatic fever in any given population. Data presented in Figure 4 suggest a significant protective effect of the culture program.

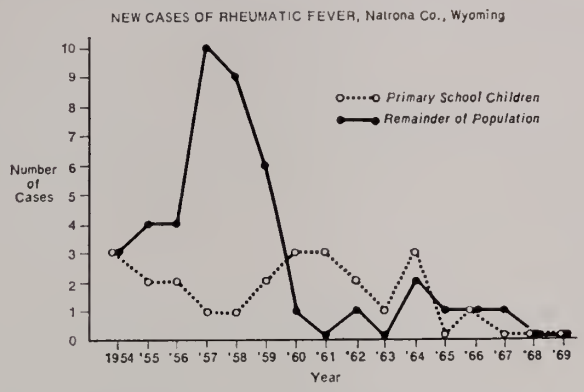


Fig. 4—New cases of rheumatic fever in Natrona County, Wyoming. Primary school children are included in the surveillance and treatment program while, until 1960, the remainder of the County was not. Subsequent to the streptococcal epidemic in the years 1957-58 and 1958-59 streptococcal control measures were extended as far as possible to include the entire population of the County. During the epidemic (1957-59) the two populations may be considered distinct.

The Natrona County protocol was subsequently applied throughout most of the State of Wyoming. Two counties did not participate in the program. In the 21 counties with a program there was one case of rheumatic fever per 24,230 people observed. In the two counties without surveillance there was one case per 6,250 people observed.

The Papago project has provided an unparalleled opportunity to document incidence of new cases of rheumatic fever before and after implementation of control measures. A computerized health delivery system has been organized with the cooperation of the Papago tribe and the United States Public Health Service so that all major illnesses are stored in a data bank and systematically reviewed. Every new case of rheumatic fever on the reservation has been checked and validated by a cardiologist. In the six years preceding the organization of the streptococcal control program 4 to 12 new cases of rheumatic fever were detected annually in the 7,800 inhabitants of the Sells, Arizona, service area. The streptococcal control program was organized in January of 1973 and became fully effective by the fall of that same year, combining school surveillance programs and intensive family followup of positive cultures. During the winter of 1973 and 74 for the first time in recorded medical history there were no new cases of rheumatic fever among the Papago Indians of the Sells service area (Figure 5).

NEW CASES OF ACUTE RHEUMATIC FEVER PER YEAR
BY NUMBER OF INDIVIDUALS, SELLS SERVICE UNIT

YEAR	NUMBER OF INDIVIDUALS	
1969	7	(Does not include a complete year of out-patient information.)
1970	12	
1971	6	
1972	4	
1973	6	(Last date of new case diagnosis was on 5/29/73)
1974	0	

Fig. 5—New cases of rheumatic fever among 7,800 Papago Indians in the Sells Service Unit area. Streptococcal control measures were begun in January 1973 and became effective throughout the whole population by late summer of the same year with intensive school surveillance programs in the year 1973-74. 1974 appears to be the first year in the history of this tribe with no new cases of rheumatic fever.

Other Benefits

Mass education seems to be accomplished by such programs. Children are systematically taught the significance of streptococcal pharyngitis and the importance of culturing. Involvement of parents in throat culturing heightens the educational impact. Physician participation in such programs, again, heightens the level of professional awareness in diagnosing and treating streptococcal disease. The educational benefits of such a program may well be one of its chief assets.

Cost

In the Wyoming program financial savings have been accomplished by mass culturing and by use of volunteers. Total cost of each culture processed by fluorescent antibody microscopy has been approximately 20¢ per culture (not including rent, light and heat which are furnished). Actual costs in similar programs, such as Colorado, have ranged up to 50¢ per culture.

In the Wyoming program, where culturing is very intensive, the cost is less than $1 per pupil per school year. Considering that the cost of lifetime care of a case of rheumatic heart disease will be in the neighborhood of $25,000, this kind of surveillance program may be justified on an economic basis alone without reference to the personal tragedy involved for victims of rheumatic heart disease.

This type of intensive effort may not be justified in areas and in populations in which streptococcal disease is not a significant health problem. Streptococcal disease and its sequelae constitute major health problems primarily among minority groups, among the poor, and in certain discrete geographic areas.

Conclusions

1. Rheumatic fever is predominantly a disease of school children during the school year in temperate zone populations. Attempts at control of streptococcal disease should be directed toward that population.

2. A well organized surveillance and treatment program can lower the rate of streptococcal isolation and alter the incidence of streptococcal infection in a school population.

3. Data now emerging suggests that these programs are effective in preventing rheumatic fever.

4. The program should be considered for high-risk populations, i.e. school children living in endemic areas, groups subject to repeated streptococcal epidemics, the poor and minority groups. Education of medical and lay public may represent one of the chief yields of this type of program.

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Southern Minnesota Medical Association

The annual meeting of the Southern Minnesota Medical Association will be held September 27, 1975, at the Holiday Inn in Mankato. Contact: Ethel A. McClane, 1726 North Fourth Street, Mankato 56001.

Role of Throat Culture Facilities

Laboratory Diagnosis of Streptococcal Disease

JOHN J. REDYS*

Relatively few states have extensive streptococcal throat culturing programs despite the widely held view that implementation is important to the primary prevention of rheumatic fever. Economic factors are significant deterrents to broader involvement. Of the several potential culturing providers discussed, physician's office testing receives special emphasis.

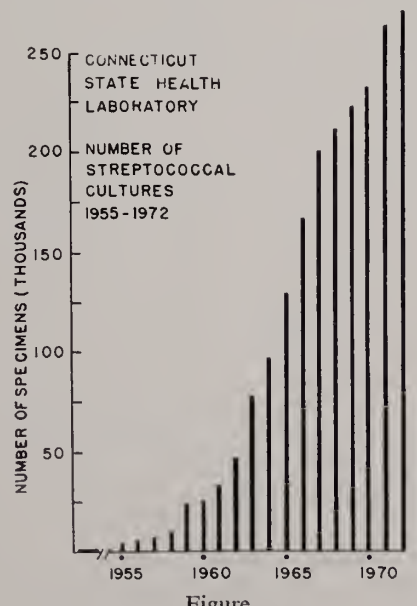
RHEUMATIC FEVER is preventable through proper antibiotic treatment of patients with streptococcal infections of the throat. Patients with nonstreptococcal infections do not develop rheumatic fever. The only way to diagnose streptococcal pharyngitis accurately is to do a throat culture. Six generally known sources provide throat culturing services in this country. (1) State Health Departments, (2) Municipal and County Health Departments, (3) Community Hospitals, (4) Independent Commercial Laboratories, (5) School clinics, (6) Physicians' offices.

According to Jackson[2] the total culturing effort in the United States and Territories approximated 3.1 million in 1971. State Health Departments produced 61% of this total; the remainder was produced by the other five facilities. It is difficult to estimate how many cultures should be done, but Phibbs[4] and Zimmerman[5] each found that extensive culturing significantly reduced prevalence of Group A, Streptococci in school populations.

Although state public health laboratories with trained microbiologists should be in the best position to provide low cost and accurate throat culture services, nearly half of the states offer little or no service of this type[6] as will be seen in Table 1. While state laboratories may have the potential to deliver work at a low per specimen cost, the lack of money required to operate large scale programs probably will remain a significant deterrent. In the state of Connecticut the per specimen cost is estimated to be $1.00: 48¢ for labor, 40¢ for supplies and 12¢ for overhead. (Table 2).

In 1973 approximately 287,000 specimens were processed. The throat culture program in Connecticut represents nearly 15% of the annual laboratory budget. There are more populous states with smaller laboratory budgets. A streptococcal program of Connecticut's magnitude conceivably could consume the entire health department budget of some states. The matter of logistics and intransit delays is also a problem for a centralized service. In Connecticut approximately 40% of the specimens take 48 hours or more to arrive in the laboratory in Hartford, despite the fact that no point in Connecticut is more than 75 miles away.

City health department laboratories in Connecticut examine approximately 50,000 cultures



Figure

*Assistant Director Laboratory Division, Connecticut State Department of Health, Hartford, Connecticut.

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yearly. Several laboratories are in the process of stopping their throat culture programs because of lack of funds. It should be pointed out that municipal health department laboratories cannot deliver results anymore rapidly than the State Laboratory because it takes as long to mail a specimen across town as across the state.

Hospital and independent laboratories charge an average of $6.00 per throat culture. Costs associated with such services make this type of throat culture facility an unlikely large scale provider.

School clinics and physicians' offices are in a good position to provide large scale throat culture testing. However, since the laboratory work is usually delegated to a non-bacteriologist, the accuracy of this approach has been questioned. Reports regarding the effectiveness of culturing in the physicians' offices have varied from 66% accurate[7] to 80-90% accuracy.[8-12] The value of school involvement as a means of controlling streptococcal infections was amply shown by Phibbs and Zimmerman.[4,5] Unfortunately, to date neither the school clinic nor physician's office approach appears to have been extensively implemented.

Several years ago we began the search for a method to enable the non-bacteriologist to interpret throat cultures simply and accurately. What eventually evolved was a throat culture kit and incubator which is highly promising for physician's office and clinic use.

The container for the medium is a hinged plastic case with overall dimensions approximately 1″ x 3″ x ¼″ (⅛″ bottom ⅛″ top). The medium is a standard tryptose-sheep blood agar containing nalidixic acid (15 mcg/ml) and neomycin (30 mcg/ml) as selective inhibitors. These inhibitors allow streptococci to grow while gram negative rods, staphylococci and neisseria are inhibited.[13-17] A strip of cellophane is placed on the agar after solidification. This film enhances shelf life during storage but, more importantly, provides the required reduced oxygen tension following inoculation of the throat swab on the surface of the agar. Thus, agar stabbing, cumbersome pour plates or anaerobic apparatus become unnecessary.

The incubator is an ordinary glass-top electric food warming tray modified to hold a temperature of 35°C. This is accomplished through the use of a 24 V. step-down transformer and an ordinary fish-tank thermostat. The incubator cover is made of plexiglass.

In use, the kit is opened, the cellophane is rolled back and the surface of the medium is rubbed with the swab specimen. Inoculation is simplified since wire streaking needles and bunsen burners are unnecessary. At this point, a bacitracin disc may be applied near the center. The cellophane is re-positioned smoothly on the agar sur-

TABLE 1
Streptococcal Throat Culture Activity Rate of State and Territorial Laboratories for 1972*

Over 100*		51-100*		26-50*		11-25*		6-10*		5 or less*	
Wyoming	311	Connecticut	81	New Hampshire	43	Tennessee	25	Wisconsin	10	Louisiana	5
Colorado	114	Vermont	52	Hawaii	39	Oregon	25	Ohio	10	Illinois	4
				Rhode Island	36	Alaska	23	Iowa	9	District of Columbia	3
				Massachusetts	29	Maine	15	Kansas	9	Montana	3
				North Dakota	28	Idaho	14	West Virginia	8	Arkansas	3
				Utah	26	Virgin Islands	14	So. Dakota	8	Florida	2
				Mississippi	26	Michigan	14	Missouri	7	Georgia	2
						Alabama	13	Arizona	7	Kentucky	2
						Virginia	13	No. Carolina	6	Guam	1
						Puerto Rico	13	Oklahoma	6	Delaware	<1
						Maryland	12			Minnesota	<1
										Nebraska	<1
										Nevada	<1
										New Jersey	<1
										New York	<1
										S. Carolina	<1
										Tennessee	<1
										Washington	<1
										Pennsylvania	<1
										California	<1

*No. of cultures per 1,000 of population.
†HEW, PHS CDC, Atlanta, Georgia, Consolidated Annual Report, F.Y., 1972.

face and, if a disc has been used, it should be pressed gently into the agar.

In our initial evaluations, several pediatricians with no expertise in office culturing were invited to participate. Office nurses or assistants were included when instructions were given. Samples of positives and negatives were shown and color pictures were left for reference. During the evaluation swabs were collected in duplicate. One was tested in the physician's office, the other was mailed to the central laboratory in the standard mailer. Cultures from both sources were saved and reviewed concurrently before discarding. This comparison involved only the detection of beta hemolytic streptococci. In over 1000 specimens tested in duplicate, an agreement between office cultures and State Laboratory processed cultures was 95.4 percent. Disagreements usually occurred with specimens containing small numbers of the hemolytic streptococci. The number of disagreements was nearly equal: 22 and 24.

On rare occasions group A streptococcal strains grow slowly but hemolysis became clearly evident in 36-48 hours. For this reason, cultures are held for an additional 24 hours at room temperature before discarding.

The system now has been implemented in Connecticut. State physicians who have been sending over 10-12 cultures per week to our laboratory are the main target. The kits and incubator are being furnished to them at cost: i.e., 35 cents per kit and $20 for the incubator. Twenty physicians and three hospital pediatric departments are in the program. By encouraging the large users of our state streptococcal service to adopt the office culture system, we anticipate at least an equivalent or an increase in the total number of cultures performed but at lower cost to the state. For kit users delays due to mailing will no longer exist, so antibiotic therapy justifiably may be withheld until cultural result becomes available the next day.

The streptococcal "office culture" program is

TABLE 2
Estimated per Specimen cost of Throat Culture Examinations for Group A Streptococci

Supplies		
Mailing outfit (silica gel and enclosures)	$ 0.11½	
Prenumbered tapes (2/specimen)	0.01	
Sheep blood agar plates	0.14	
Slides and cover slips	0.03½	
Todd-Hewitt broth	0.02	
Group A FA conjugate	0.02	
Stationery, copies and stamps	0.06	
Sub-Total		$ 0.40
Labor		
Packaging and mailing outfits to doctors	0.02	
Sorting and numbering specimens	0.05	
Processing swabs	0.12	
Examination of blood plates and record results	0.05	
FA smear preparation and stain (35/100)	0.05	
FA examination	0.05	
Clerical (mailing, telephoning and filing)	0.14	
Sub-Total		$ 0.48
Miscellaneous and Overhead		
Administrative and research and development	0.02	
Telephone—(20/100 are phoned to local Heart Asso.)	0.05	
Equipment—FA ($1,600. spread over 10 years plus $200./year for bulbs—250,000 specimens per year)	0.01	
Sub-Total		$ 0.12
Total		$ 1.00

TABLE 3
Office Strep Throat Culture Kit vs. Mailing in to State Laboratory*

No. Drs.	No./% of duplicate cultures	Agreement — No./% State + M.D. +	State − M.D. −	Total	Disagreement — No./% State + M.D. −	State − M.D. +	Total
4	1001	313	642	955	22	24	46
	100%	31.2%	64.1%	95.4%	2.2%	2.4%	4.6%

*Beta hemolytic streptococci.

seen as an ancillary measure and not replacement for the strong central streptococcal laboratory now in existence. The State Laboratory is expected to continue to: (1) examine throat swabs for physicians collecting fewer than 10-12 per week; (2) act as a streptococcal reference center; (3) teach other laboratories; (4) monitor the office culture program.

The emphasis so far has been on quantity. A few comments, germane to quality of the work furnished by streptococcal throat culture facilities might be appropriate at this time. Throat swabs not plated immediately can be held effectively in a tube in the refrigerator for several hours or overnight. Outside the refrigerator, recovery becomes less certain unless special holding methods are employed. Semi-solid transport media (Stuart's or Amies), Silica gel crystals* or "Culpak" filter paper strips† work well. Silica gel crystals are available commercially in individual foil packets into which the swab is inserted after collection. A laminated manila-to-foil envelope is the second protective container for the swab held in the silica gel pouch. The third portion of the package is a manila envelope which carries the mailing address.

Blood of animals other than sheep is not recommended for culturing streptococci. A glucose free base without infusions is preferred. Plates which are too thick or contain too high a concentration of blood may make recognition of beta hemolytic streptococci difficult. We add 5% blood with a 33-36% hematocrit. Approximately a 12 ml. pour per standard plastic dish is used. We recommend an expiration time of five weeks. Some commercial blood plates may contain agar concentrations up to 2.0 percent instead of the conventional 1.5 percent in order to improve shipping characteristics. We have no knowledge what effect this has on the production of hemolysis by beta hemolytic streptococci.

Incubation of the blood agar inoculum under reduced oxygen tension should be carried out to avoid missing positives. CO_2 incubation (candle extinction method) is inadequate. One recent study[18] indicated that 15/31 group A streptococci would have been missed with 5% CO_2 incubation alone and also indicated that 95% were found by anaerobic incubation, 84% by an agar overlay technique and only 62% by the "stab" method. Pour or overlay plates are cumbersome and subsurface nonstreptococcal colonies can be confused with streptococcal colonies. The agar stab or agar cut method enhances hemolysis, but may be difficult for the inexperienced technician to ascertain if hemolysis was due to a streptococcus or another organism. Anaerobic apparatus is effective but inconvenient. With the kits the cellophane sheet method described was effective and simple.

Questions occasionally are received regarding effectiveness of the fluorescent antibody method (FA) for group A streptococci. It is sensitive but tedious and time consuming. If automated hardware for processing throat specimens by FA ever becomes available, it could be the method of choice for large scale testing.

*Available from Carter, Rice, Storrs and Bemont, Inc., East Hartford, Connecticut 06008.

†Available from Becton, Dickinson and Co., Oxnard, California 93030.

Summary

Untreated upper respiratory streptococcal infections may lead to rheumatic fever. Throat culturing facilities are important to primary prevention of rheumatic fever because they can furnish the Clinician with laboratory results essential to an accurate diagnosis and prudent use of antibiotics. The amount of culturing presently being done may be far less than is necessary to control streptococcal infections. A number of state laboratories provide virtually no streptococcal services. Costs of these services on a large scale basis is the main deterrent. Physician offices and school clinics are in an ideal position physically to intensify culturing efforts in both active and inactive areas. Accuracy of results emerging from these settings may be opened to question. Use of a medium selective for streptococci in conjunction with an expedient which provides reduced oxygen tension to the inoculated surface can enhance accuracy in such facilities. Such an approach has been evaluated in Connecticut with success and is being implemented gradually.

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* **Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

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Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

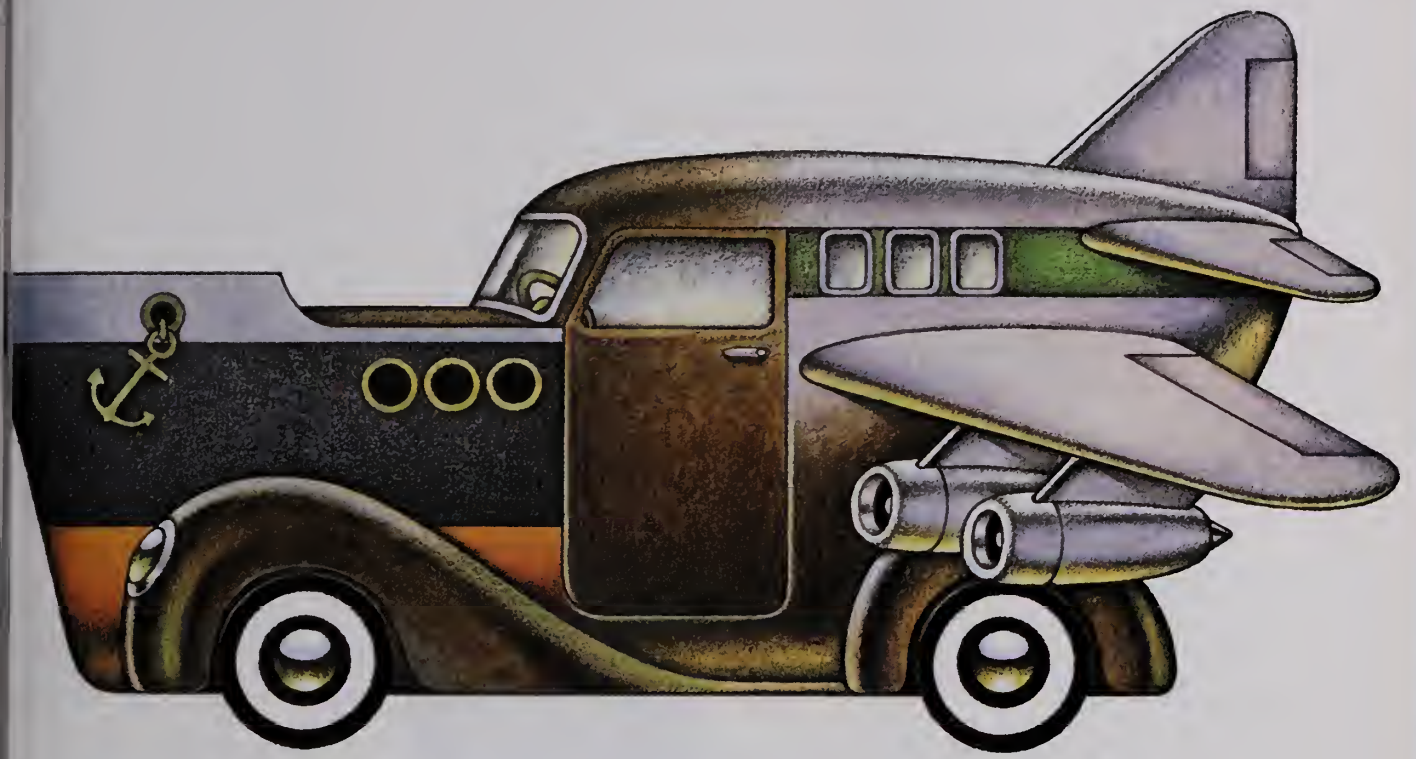
Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

CONTRAINDICATIONS. Administration of Antivert during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

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Antivert®/25 Chewable Tablets
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for motion sickness

Opinion & Dialogue

Should a specially prepared package insert be made available to patients?



Dr. Alexander M. Schmidt
Commissioner,
Food and Drug
Administration



Dr. James H. Sammons
Executive Vice President
of the American
Medical Association

The idea of a so-called pati
package insert has been around
a long time. Many physicians alr
use written instruction sheets to
provide patients with informatio
about the drugs they are taking.
some physicians give verbal inst
tions; but in too many instances
these are what I call eye-glazing
ercises. I have seen patients sit
glazed eyes listening to a rapid-f
lecture by a hurried physician w
has 20 people out in his waiting
room. These patients aren't give
sufficient understanding and th
fore do not follow instructions. S
think the idea of an official pack
insert for patients is a good one.
Perhaps we should really think c
this kind of information simply a
extension of drug labeling.

The benefits of patient involvemet

Many physicians may not r
ize how frequently a patient obta
his drug information from Aunt
Tillie or the next door neighbor.
this information is almost alwa
bad or irrelevant to the case at h
Furthermore, the incentive to gc
along with a prescribed program
slim if the only reading matter th
patient receives, along with his p
scription, is a bill.

As an educator I am impre
by the principle that the best wa
get someone to do something is
involve him in the process. So th

I think there are advantage
well as some real disadvantages
a patient package insert. When yu
begin to use semi-medical or me
cal terms to describe complicatins
or possible sequelae of disease c
treatment, you may frighten the a
tient—particularly since the mo
highly sophisticated patient is n
the one who is going to read the
sert. The patient who will read it
the one most susceptible to frigh
and confusion by the language.

On the positive side, a pack
insert will probably give the pati
better insight into why he is bein
treated the way he is, and it may
give the physician a little bit mo
time. But it does not remove fro
the physician the need or obliga
to explain the insert.

Some pitfalls in the inclusion of side effects

Certainly a patient should
warned of the possibility of serics
side reactions—to know what th
real dangers are. But it doesn't d a
bit of good to indicate that a pat n
on oral penicillin may develop a
rash, itching, or a drop in blood
pressure. Or that he may faint. I
think the real danger is that frig
engendered by the insert may p
sibly outweigh the potential goo

n purpose of drug information
ne patient is to get his cooperain following a drug regimen.

aration and distribution of nt drug information

We would hope to amass inforon from physicians, medical eties, the pharmaceutical industnd centers of medical learning. ultimate responsibility for uni- labeling must, however, rest the Food and Drug Administra- There is nothing wrong with agency saying, "this informais generally agreed upon and efore it should be used," as long ur process for getting the inforon is sound.

Distribution of the information problem. In great measure it ld depend on the medication in stion. For example, in the case injectable long-acting progesne, we would think it mandatory sue two separate leaflets—a t one for the patient to read begetting the first shot and a long to take home in order to make a sion about continuing therapy. is case, the information might ut directly on the package and emovable at all. But for a mediin like an antihistamine this rmation might be issued sepay, thus giving the physician the n of distribution. This could erve the placebo use, etc.

It is in the distribution of patient information that the pharmacist may get involved. As professionals and members of the health-care team and as a most important source of drug information to patients, pharmacists should be responsible for keeping medical and drug records on patients. It is also logical that they should distribute drug information to them.

Realistic problems must be considered

We have to expect that the introduction of an information device will also create new problems. First, how can we communicate complex and sophisticated information to people of widely divergent socioeconomic and ethnic groups? Second, what will we say? And third, how can we counteract the negative attitude of many physicians toward any outside influence or input? Hopefully the medical profession will respond by anticipating the problems and helping to solve them. Assuming we can also solve the difficulty of communicating information to diverse groups throughout the United States, our remaining task will be the inclusion of appropriate material.

What information is appropriate?

In my opinion, technical, chemical and such types of material should not be included. And there is no point in the routine listing of side effects like nausea and vomiting which seem to apply to practically all drugs, unless it is common with the drug. However, serious side effects should be listed, as should information about a medication that is potentially risky for other reasons.

Other pertinent information might consist of drug interactions, the need for laboratory follow-up, and special storage requirements. What we want to include is information that will help increase patient compliance with the therapy.

Positive aspects of patient drug information

Labeling medication for the patient would accomplish a number of good things: the patient could be on the lookout for possible serious side effects; his compliance would increase through greater understanding; the physician would be a better source of information since he would be freer to use his time more effectively; other members of the health-care team would benefit through patient understanding and cooperation; and, finally, the physician-patient relationship would probably be enhanced by the greater understanding on the part of the patient of what the physician is doing for him.

---

the doctor can remove that fear 0 or 30 minutes of conversation.

I'm not suggesting that we hold any information from the nt because, first of all, it would tally dishonest and secondly, it d defeat the very purpose of the t. I do think that a patient on the control pill should know about ncidence of phlebothrombosis.

If you're going to tell a patient ncidence of serious adverse reons, then you have to tell him a concerned medical decision made to use a particular mediin in his situation after careful sideration of the incidence of plications or side effects.

tionally unstable patients pose ecial problem

There are patients who, be- e of severe emotional problems, d not handle the information ained in a patient package in- Yet if we are going to have a age insert at all, we just can't two inserts. I think we might ly have to tell the families of e patients to remove the insert the package.

l implications of the patient age insert

Just what effect would a patient package insert have on malpractice? We could try to avoid any legal implications by pointing out that the physician has selected a particular medication because, in his professional judgment, it is the treatment of choice. For instance, you can't tell everyone taking antihistamines not to work just because a few patients develop extreme drowsiness which can lead to accidents. And what about the very small incidence of aplastic anemia rarely associated with chloramphenicol? If, based on sensitivity studies and other criteria, we decide to employ this particular antibiotic, we do so in full knowledge of this serious potential side effect. It's not a simple problem.

How do we handle an insert for medication used for a placebo effect?

With rare exceptions, physicians no longer use medications for a placebo effect. This question does raise the issue of how a patient may react to receiving a medication without a package insert.

Preparation of the package insert

The development of the insert ought to be a joint operation between physicians, the pharmaceutical industry, the A.M.A. and the F.D.A.

I view the A.M.A.'s role as a coordinator or catalyst. It is the only organization through which the profession as a whole, irrespective of specialty, can speak. It has relatively instant access to all the medical expertise in this country. And it can bring that professional expertise together to ensure a better package insert. The A.M.A. can work in conjunction with the industry that has produced the product and which is ultimately going to supply the insert.

I don't think we should rely, or expect to rely, on legislative committees and their nonprofessional staffs to make these decisions when it is perfectly within the power of the two groups to resolve the issues in the very best American tradition—without the government forcing us to do it. I think the F.D.A. has to be involved, but I'd like them to become involved because they were asked to become involved.

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Editorials

Control of Group A Streptococcal Infections

The Community's Responsibility

FOR THE LAST SEVERAL decades the group A beta hemolytic streptococcus, because of its unique ability to cause non-suppurative sequelae in heart, kidney, joints, skin and central nervous system has aroused intense interest in studying and in ultimately solving the riddles of the epidemiology and pathogenesis of these sequelae. From basic laboratory research knowledge about the organism itself and the immunological response to streptococcal infections has accumulated exponentially. Epidemiological studies have also provided essential data. Initially, investigations of streptococcal upper respiratory tract infections were of primary interest. In the last ten years the same zeal has been applied to studies of streptococcal pyoderma and its major non-suppurative sequela, acute post- streptococcal nephritis.

These research efforts, both in the laboratory and in the "field", have provided important new information making it easier to enumerate the indictments against the group A streptococcus for its role in producing disease, information which has proven practically useful in control of streptococcal infections and their sequelae. Furthermore, data such as those from Gordis' studies have suggested that with basic knowledge available and with a practical method of delivery of health care services, the incidence of rheumatic fever, for example, might be reduced.[1]

The plea for wide-spread implementation of information gained from both laboratory and "field" studies in the community control of streptococcal infections is by no means a new one. Suggestions for guidelines for community action by both the American Heart Association[2] and the Intersociety Commission for Heart Disease Resources[3] have already prompted persuasive editorial comment.[4-5]

What perhaps deserves additional emphasis at this time is that it is becoming apparent that certain specific groups in each community may deserve more intense attention. In urban areas, it is among the disadvantaged populations of the inner city where the incidence of acute rheumatic fever appears to be greatest.[6] It is among economically and socially disadvantaged populations that streptococcal pyoderma and skin-associated nephritis appear more likely to occur.[7-8] Last, but not least important, streptococcal infection should be considered an "occupational disease" of school children since it occurs with a high frequency during the school years among all socioeconomic groups.[9]

Although concern for "streptococcal control" has been given lip service in many communities, perhaps a reevaluation of previous efforts should be undertaken and emphasis should now be placed on directing the attention of responsible public authorities and appropriate health organizations to the specific problems of streptococcal infections in each community. Each community should be encouraged to identify and carefully document its own high risk groups and to focus its efforts especially on these groups whether this be suburban school children, urban inner city populations, or rural migrant workers. To seek to accomplish this is not unrealistic, for it has been shown that with proper motivation and resources a community can undertake programs in streptococcal control. One often quoted example has been the school programs in Casper, Wyoming.[10] As with any health program, the responsibility would appear to lie not only within the practicing medical community, but especially with school health and public health authorities and even consumer groups.

It was the purpose of the Conference on Community Control of Streptococcal Infection held in Minneapolis in June of 1974 and jointly sponsored by the American Heart Association and the Minnesota Heart Association to bring together from around the country those with experience with this problem for presentation and discussion of practical approaches to community control of streptococcal disease. In this issue of MINNESOTA MEDICINE are included seven of the formal presentations from that conference. These papers outline current thinking about several aspects of streptococcal infections including the bacteriology of the organism, the epidemiology of streptococcal infections and their sequelae, newer concepts of the pathogenesis of rheumatic fever and practical aspects of community control of these infections. These papers may serve as useful guides in the planning and implementation of similar programs elsewhere.

Edward L. Kaplan, M.D.*
Guest Editor

*From the Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota. Supported in part by the Dwan Family Fund.

Address fore reprints: Dr. Edward L. Kaplan, Department of Pediatrics, University of Minnesota, Minneapolis, Minnesota.

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COVER PHOTOGRAPH

"Willamette Valley"

Dr. J. W. Burnett took the cover photo on Ektachrome-X film at 1/250 sec. and f/16. It was taken in the Willamette Valley in western Oregon while Dr. Burnett and his wife were on a holiday. They happened on the scene just by chance along the side of a little country road, and Dr. Burnett told the Editors that the farmland there is much like that along the Minnesota and Cottonwood Rivers of his hometown area, Brown County in Minnesota.

A graduate of the University of Minnesota, Dr. Burnett completed his internship at Hennepin County General Hospital and has worked nearly three years in the Emergency Room at the Metropolitan Medical Center. He is presently doing an orthopedic residency at the Minneapolis Veterans' Hospital.

Dr. Burnett has done professional and semi-professional photography since the age of 16 and was a staff photographer with the MINNESOTA DAILY at the University of Minnesota as an undergraduate.

Fifty Year Club

LIKE BEN HECHT the fifty year club members of the MSMA are children of the century. They were of an age to have seen service in World War I if no more than SATC (Students Army Training Corps) attending classes at the University in ace bandage type leggings and high hooked collars. Most of them belong to Medical School Class of 1925. Forty-two were inducted into the club at the annual meeting of the MSMA last May. The list of these distinguished gentlemen is published in this issue.* Their classmate, Cecil J. Watson, is singled out for a more extensive biographical sketch by Robert Howard.† The graduates in 1925 probably could not then afford the illustrated Franklin coupe. But it was THE car of the doctor of the twenties. The following excerpts from MINNESOTA MEDICINE of 1925 are intended to give the flavor of the time. The editor's notes are in brackets.

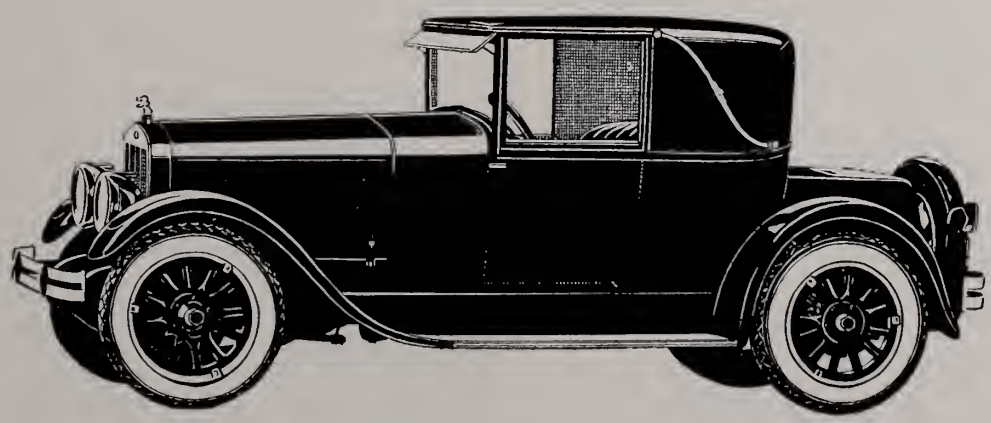
"From Jan. 1, 1924, until Jan. 16, 1925 there occurred 286 deaths from smallpox in Minneapolis, 39 of these deaths having occurred since Jan. 1, 1925. During the same period 20 deaths occurred in St. Paul." [Minnesota Health department statistics for the last 32 years indicate no deaths from small pox in Minnesota, and no cases reported in the United States since 1949. It is unlikely that even one in a hundred present day physicians has seen a case of smallpox.]

"Newer ideas of Infection in Nervous Disease: . . . First focal infection. For the past few years the medical profession has been demonstrating its interest in this field. There have been enthusiasts who advocated the indiscriminate pulling of teeth and so we see young men and women of 25 or 30 wearing one or more plates. Others have insisted that the tonsils must be the root of all evil and have advised removal of these organs 'ad libitum'. The writer has recently seen three cases of violent insanity clear up almost miraculously, two following extraction of badly abscessed teeth and one following the removal of diseased tonsils." [The highwater mark in the flood of articles on focal infections must have been 1925 although some of these "newer ideas" surely persist to this enlightened day.]

"The average mortality following prostatectomy when pre-operative and post operative treatment are under the direction of an urologist, is about Three per cent. The mortality in some hospitals where general surgeons and general practitioners operate on prostatic patients is as high as 20%." [Prostatectomy of 1925 was indeed a fearsome procedure and 20% mortality no exaggeration. I recall lectures given a few years later by a urologist who demonstrated his technique of cutting off the end of the rubber glove over the right index finger exposing the fingernail which was his tool to dissect out the prostate.]

"Three Duluth Physicians, Drs. R. S. Forbes, J. R. Manley, and J. E. Power will leave shortly, with their families, for from three to six months special study in Europe. Dr. Power expects to devote his time to a study of eye, ear, nose, and throat; Drs. Forbes and Manley to gynecology and obstetrics. All of them expect to follow the

*See page 627.
†See page 629.



1925 Franklin air-cooled coupe

precedent set by many other Minnesota physicians and intend to do their preliminary work in Vienna. The men interested in Gyneeology and obstetries expeet to visit Dublin." [The eustom of a few months postgraduate training on the eontinent was de riguer for the young practitioner in the early years of the eentury and apparently was still a stimulus to travel in 1925.]

"The HORMONE OF THE PARATHYROID GLAND—CHANGES IN THE BLOOD SERUM CALCIUM OF THYROPARATHYROIDECTOMIZED DOGS. By Adolph M. Hanson, M.D. Faribault, Minnesota." [This paper will not be summarized here. Dr. Hanson laboring alone made fundamental diseoveries of the parathyroid hormone.]

"Diseussion (of a paper on abdominal surgery) by Dr. J. P. Schneider, Minneapolis: Mr. Chairman, I presume my exeuse for diseussing a surgieal paper in the surgical seetion is that I am firmly eonvineed that an internist unassociated intimately with a surgeon is an unsafe internist, and likewise that a surgeon unassoeiated with an internist is an unsafe surgeon . . . I am sure that the average unassoeiated internist when eonfronted with this urgent surgical problem (perforated gastrie uleer] would be inelined to be too dilatory and spend too mueh valuable time in arriving at a diagnosis."

"FOR SALE: General praetice in southern Minnesota village; good dairy farming eommunity; three tributary towns without physieian; cash reeeipts last year $9,000. Good man will make money from the start."

"EDITORIAL—Twelve Hour Hospital Nursing. The recent deeision of the nurses and hospitals in the fourth distriet of the Nurses State Assoeiation to substitute the twelve-hour shift for private nursing in hospitals (the ehange does not affeet nursing in the home) for the eustomary twenty-four hour shift is a step in keeping with the general trend throughout the eountry. The twelve hour shift, however, has decided disadvantages as well as advantages."

The people of Minnesota owe you Fifty Year Veterans an unrepayable debt for your lifetime of serviee. The best we ean do is aeknowledge it and deelare our gratitude.

Reuben Berman, M.D.
Editor Emeritus

Letter to the Editor

The Errant Editor

Dear Editor:

I endorse enthusiastieally your message in the June issue.* But you might have added one more item, namely, eheek your arithmetie.

You state that a revision of a 16-word sentenee to an 8-word one is a 100% deerease. Aetually, it's a 50% deerease. Going from 8 to 16 would have been a 100% increase. From 16 words to 7 is 56% deerease (not 130%) and 18 to 7 is a 61% decrease (not 160%).

Charles A. Owen, M.D.
Mayo Clinic

*Page 437. Editor's Notebook: Shortening Manuscripts.

Editor's Note: You are absolutely right. I was wrong, which proves I'm not a calculating man.

Practical Dermatology for Primary Care Physicians
August 22-24, 1975

A postgraduate education eourse on practieal dermatology will be offered by the Department of Dermatology and the Offiee of Continuing Medieal Education of the University of Minnesota in downtown Minneapoiis on August 22, 23, and 24, 1975. The course will stress therapy of common skin disorders and eutaneous manifestations. For further information, contact the Offiee of Continuing Medieal Edueation, Box 293 Mayo Memorial Building, University of Minnesota Hospitals, Minneapolis, Mn. 55455.



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Cecil James Watson: An Encomium

I HAVE BEEN told that among surfers there is a belief that every ninth wave is appreciably larger than those that preceded it. Thus the ninth wave is awaited and ridden into shore with special zest. Further, this belief goes, after eight such ninth waves have come in, the "ninth ninth" will be even larger than the other "ninths", towering above all those surrounding it.

Whether this belief has any basis in fact I must leave to the oceanographer. I am certain, however, that human endeavor is marked by the occasional emergence of a towering figure, a "ninth ninth", if you will. Such a figure is Cecil James Watson, whose half-century of membership in the Minnesota State Medical Association is being recognized and honored this year. No one has wielded greater or more constructive influence over the development of internal medicine in Minnesota during this period than Cecil. Nor has his influence been limited to the local scene. His research and his accomplishments in medical education have brought him national and, indeed, international recognition.

Cecil's father, James Alfred Watson, was a native of Ireland, who migrated in his youth to Canada, where he attended medical school. Subsequently he migrated once again, to Minnesota where he practiced first in a rural setting. Later, after postgraduate study in Europe, he practiced in Minneapolis, specializing in diseases of the eye, ear, nose, and throat. Cecil was born in Minneapolis and grow up in its Kenwood district. During his college years, Cecil was torn between literature and medicine as possible career choices. Fortunately for medicine, he chose the latter, but his love of and familiarity with literature are evident to all who work closely with him.

He entered the University of Michigan Medical School for his first year of medical school, but returned thereafter to the University of Minnesota, where he encountered among others, the late, beloved, E. T. Bell, certainly another "great" in the history of medicine in Minnesota. At least in part under Bell's influence, Cecil entered the field of pathology, combining this study with the regular medical course and ultimately acquiring both the M.D. and Ph.D. degrees.

Following graduation, he served for two years as a pathologist at the Minneapolis General Hospital, assuming responsibility for the clinical laboratory. During this period, his lifelong interest in the bile pigments began to develop, an interest that continued to grow during the subsequent two years, during which he was responsible for the laboratory for a newly formed clinic in Minot, North Dakota.

The next two years, 1930-1932, proved to be a watershed period for Cecil and his wife, the former Joyce Petterson, whom he had married approximately five years before. With the help of Dr. George Fahr, a pioneer professor of medicine at the University of Minnesota, Cecil successfully sought an opportunity to study with Hans Fischer, Nobel Prize winning organic chemist, in Munich, Germany. Cecil proved to be an apt pupil. Among his accomplishments during this period was the solution of the difficult problem of isolating stercobilin from the feces. During the Munich period he also had an opportunity to attend the stimulating clinics of Dr. Friedrich Mueller, the distinguished Professor of Medicine in Munich. He and Joyce also took full advantage of the social, cultural, and recreational opportunities of Bavaria.

Returning to the United States in 1932 to find the country in the midst of the depression, he decided to enter clinical medicine and to apply his newly gained knowledge of bile pigment chemistry to problems at the bedside. He served as a resident in medicine for three years, first under George Fahr and then under Hobart Reimann. His outstanding capabilities as clinician, teacher, and investigator were quickly recognized by University of Minnesota Medical School authorities, and in 1936 he was made Director of the Division of Internal Medicine, at that time a component of a larger Department of Medicine, which also encompassed neuropsychiatry and dermatology and which was headed by the late J. Charnley McKinley, a neurologist. In 1943 the Division of Internal Medicine was made a full Department, and Cecil was named its head, a post that he held until 1966. During this period the depart-

ment grew remarkably in both size and depth of interest and gained a national reputation as a department effectively combining academic excellence with sound teaching of internal medicine. Cecil's personal research interests continued and broadened to include not only the hemoglobin breakdown products, the bile pigments, but the hemoglobin building blocks, the various porphyrin compounds, as well. Today, of course, he is recognized as having made monumental contributions to our knowledge of porphyrin metabolism and the various porphyrias.

In 1966, with two years remaining before mandatory retirement from the University of Minnesota, he resigned as head of the Department of Medicine and, with the support and encouragement of University officials, moved the base of his operations to Northwestern Hospital of Minneapolis, where he founded the University of Minnesota Professional Unit for Teaching and Research in Internal Medicine. This move freed him from major administrative responsibilities and provided him with an excellent opportunity both to teach clinical medicine at the bedside and to continue his research. Under his guidance, the Northwestern Hospital program became well established as an effective undergraduate and graduate teaching unit, supplementing the over-all program of the University of Minnesota Medical School. Formal retirement from the University in 1968 brought about little real change in his status and, while he has subsequently given up the directorship of the Northwestern Hospital program he continues to remain very active as a Senior Consultant, and his research laboratory is busier than ever.

His many accomplishments have brought him many awards and appointments signifying special recognition. Only a few of these will be mentioned here. After World War II, he served on the Committee on Medicine and Surgery of the National Research Council and as Director of the Commission of Liver Disease of the U.S. Armed Forces Epidemiological Board. He served a term as a member of the Council of the National Institute of Arthritis and Metabolic Diseases. During his tenure as a member of the board of the American Board of Internal Medicine, he was instrumental in revising the examination system and introduced the objective type of examination. In 1959 he was made a member of the National Academy of Sciences. He has been named a Master of the American College of Physicians, and in 1972 he was awarded an Honorary Degree by the University of Munich. In 1972, he was awarded the Kober Medal of the Association of American Physicians. Perhaps his most prized award is the Regents' Professorship in Internal Medicine, bestowed upon him by the Regents of the University of Minnesota, upon recommendation of his faculty colleagues, in 1968.

No more brief recounting of biographical details, such as the foregoing, can possibly capture the essence of the career as remarkable as Cecil Watson's. For a more comprehensive biography, the reader is referred to the remarks of Richard V. Ebert, M.D., who presented the Kober Medal to Cecil at the meeting of the American Association of Physicians in 1972.* I want to use the remainder of the space allotted to me in an attempt to delineate some of those qualities that have made Cecil a "ninth ninth" among his colleagues. I have had, I believe, a most unusual opportunity, in that I have been associated with him in a rather wide variety of roles and relationships for more than 30 years, both on the University of Minnesota campus and at Northwestern Hospital. Circumstances of my own life have been such that, because of a rather protracted hiatus during which I did not directly participate in clinical medicine or teaching, I undertook not one but two periods of systematic study of internal medicine, separated by approximately 25 years. Both times Cecil was my principal mentor. Both periods constituted memorable, stimulating learning experiences. If anything, the "second time around" was better than the first. I have had an unusual series of vantage points from which to view and ponder his various qualities and characteristics, which I admire so very much.

First and most fundamental is his absolute integrity. Never will he compromise with what he believes to be the truth, and this is equally true in his personal and his professional relationships. When he does not know the answer to a question —not a frequent occurrence, I assure you—he says so forthrightly. He indulges in no professorial bluff or flim-flam.

A second quality is his insatiable curiosity. Many of us are all too ready to accept statements

*Ebert RV: Presentation of the Kober Medal for 1972 to C. J. Watson. Trans Assoc AM Physicians 85:51-58, 1972.

of facts or interrelationships, provided they seem reasonably well documented. Cecil has always insisted on knowing the *why*. If the why could not be adequately determined from a careful search of the available literature, the laboratory became the arena in which the answer was sought. This pervasive curiosity, this demand to get the why, accounts not only for the quality and quantity of his own research, but for countless important contributions to medical science made by young men and women whose investigational interest he has stimulated over the years.

Another quality setting him apart from so many of his colleagues is the breadth of his interests. In a professional community moving steadily in the direction of subspecialization, he has been able to maintain not only an interest but an expertise in the broad field of internal medicine, which enables him to delineate certain important interrelationships and to make associations that are missed by the narrow subspecialist. Further, his knowledge of science, in general, of history, and of literature, as mentioned earlier, never fails to impress his colleagues, and not infrequently proves to be of tangible significance with respect to the problem at hand.

Another prime characteristic of Cecil is that he has consistently demanded one's best performance. This has been particularly true with respect to himself, for clearly he has been unwilling to settle for anything other than his own best effort at all times, but he also obviously expects his associates to do their best, as well.

A high order of intelligence and basic good health are also characteristics that such individuals must have, and Cecil has had them in full measure. Intelligence, and, to a substantial degree, health are also factors that an individual cannot determine personally, so we can only be grateful that he was granted these necessary qualities.

Finally—but by no means least in order of importance—Cecil is always a gentleman, in the broadest and finest sense of that word. He treats patients and colleagues with courtesy and respect. His unrelenting honesty, to which I referred earlier, is not of the variety that impells him into harsh and personal confrontations with those with whose opinions he disagrees. He is truly masterful in dealing with such situations. He has, indeed, learned the art of disagreeing without being disagreeable.

Medicine in Minnesota and our nation has been vastly enriched by the participation and contributions of Cecil James Watson. I deeply treasure my own association with him. As I write these words of recognition of his fifty years of membership in the Minnesota State Medical Association, I am only happy that they are not being written as a tribute to a career that has come to an end, but rather as a salute to a great physician whose activities give every indication that his work will continue with undiminished vigor during the next decade or more.

Robert B. Howard, M.D.
Minneapolis, Minnesota

John M. LaBree, M.D.

Dr. John W. LaBree, director of medical education at St. Mary's Hospital, Minneapolis, was named Dean of the School of Medicine at the University of Minnesota, Duluth, effective September 1.

LaBree, a specialist in internal medicine with a subspecialty in cardiology, is also a clinical professor with the University of Minnesota Medical School in the Twin Cities. He has practiced medicine in the Minneapolis area since the early 1950's and is one of the ten original founders of the St. Louis Park Medical Center.

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Special Article

Rheumatic Fever: Its Public Relations and Private Life

ANGELO TARANTA, M.D.*

ALTHOUGH MANY physicians would deny the existence of a rheumatic fever problem, there are, in fact, at least three (Table 1). The first, how

TABLE 1
The Rheumatic Fever Problems

1. **Bio-medical problem: how does strep cause *it*?**
2. **Health care problem: how come *it's* not yet extinct?**
3. **Public Relations problem: how can *it* be interesting if it doesn't grow?**

does the strep cause the disease? is the one that most straight-A students have been attracted to, until recently, and that, in turn, has attracted the most grant money, until recently. It is a brain-teaser, a puzzle, and the pieces are still far from falling into place. In fact, since there is no generally accepted laboratory model, and experiments in man are difficult when not illegal, the pieces may *not* fall into place. That would be disappointing, but not necessarily catastrophic, since diseases have a way of disappearing, so to speak, on their own, or because a single critical step has been understood and controlled, or it has been controlled even without understanding. As an example, Figure 1 shows how the decline of mortality from pulmonary tuberculosis in England and Wales was related or, rather, unrelated, to some momentous and relevant discoveries. Lest I be mistaken for an obscurantist, let me hasten to say that knowledge of pathogenesis and etiology is gratifying and often useful, but that its relation to disease control is not as direct as some of us fancy.

*Departments of Medicine, New York University School of Medicine, and Cabrini Health Care Center, New York, N.Y.
Reprints: Department of Medicine, Cabrini Care Health Center, 227 E. 19th St., New York, New York.

Presented at the Symposium on Community Control of Streptococcal Infections held in Minneapolis, Minnesota, June, 1974.

Editor's Note: As will become obvious to the reader, this paper is different from the other papers published in this issue. Presented as an after dinner talk during the Symposium on Community Control of Streptococcal Infections, this allowed the opportunity for Dr. Taranta—then chairman of the American Heart Association's committee on Prevention of Rheumatic Fever—to comment on the rheumatic fever "problem" in the humorous but probing way for which he is known. We are certain that our readers will find this paper not only enlightening but entertaining as well.

The second problem has attracted quite a bit of attention recently. It has been repeatedly asked why rheumatic fever has not joined the ranks of other "disappeared" diseases, like diphtheria and polio, once effective prophylactic measures were found. Because of the persistent association of rheumatic fever with poverty, the fault rests in part with the persistence of poverty. Since medical care can be effective *despite* poverty, the fault also rests with the delivery or, rather, the non-delivery of medical care. And since the prevention of rheumatic fever *is* demanding of time and effort, the fault also rests with the methods of prevention.

Interesting as these problems are, I will not delve into them any further, for I must get into the third problem, the public relations of rheumatic fever. We all know what rheumatic fever is—or we think we know—but what are public relations? Are they anything that a disease is entitled to have, along with its other perquisites, like symptoms and signs? The *Webster* tells us:

> *Public Relations.* 1. The promotion of rapport and goodwill between a person, firm, or institution and other persons, special publics, or the community at large through the distribution of

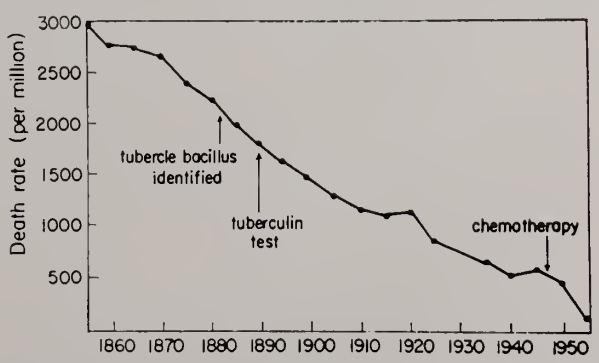


Fig. 1—Decline of mortality for pulmonary tuberculosis in England and Wales. Notice the lack of temporal relation to a series of relevant discoveries. (Permission given. Kass, E.: J Infect Dis 123:110, 1971.)

> interpretative material, the development of neighborly exchange, and the assessment of public reaction.

After reading this definition, I realized that to concoct a title like the one of this paper I must have been under the spell of an anthropomorphic delusion—to think of rheumatic fever as if it were a person, a bit like a spinster may do with a pet cat. Persons, the *Webster* says, are entitled to have public relations, and also firms and institutions, but apparently not diseases.

Yet the public relations of a disease is not an entirely outlandish concept, strictly for after-dinner speeches. A disease, after all, is not an abstract and neutral entity or concept; since it affects people, the people affected make up a special-interest group: a group that wishes, like all other groups, to be helped, or, at least, fussed over. And there is no question that there is a public reaction to disease, and that the reaction varies with the kind of disease. For a long time, the disease with the worst public relations possibly was gout—associated as it was, at least in the popular image, with a high intake of *pâté de foie gras* and high living in general (Figure 2). To sympathize with a man who eats too much or too well is difficult, however swollen his big toe may be.



Fig. 2—A gouty patient feasting and suffering. Copy of engraving by Thomas Rowlandson (1757-1827): Comforts of Bath, IX, the New Bath Guide, published by S. W. Fores, January 6, 1798, (Permission given. G. P. Rodnan: Arthritis & Rheumatism, 4:27, 1961).

As for rheumatic fever (RF), its public relations are hampered by a number of problems. I have hinted at one of them in Table 1, and I am rephrasing it here (Table 2) as problem #1: "No growth potential." Statistics are notoriously unreliable, data collection doubtlessly faulty, the definition of the disease variable, the interpretation of trends treacherous—and the decline of rheumatic fever may not be as steep as it is generally stacked up to be.

TABLE 2
PR Problems of Rheumatic Fever

1. **No growth potential**
2. **Not enough of a mystery**
3. **It always seems to strike someone else**
4. **"What have you done for me *lately*?"**

Nevertheless, rheumatic fever is hardly what financial analysts refer to as a "growth situation." This makes life hard, so to speak, for rheumatic fever, which has to compete for funds and attention not only with diseases that enjoy a steady-state, but also with those that can boast epidemics, or appear to be increasing, from venereal diseases to myocardial infarct. Also from the point of view of the "worker in the field" this "no growth" business is a hindrance: as one of them remarked to me the other day: "it is no good to be associated with a 'disappearing disease'."

The second problem is milder, but still real: not enough of a mystery. Since the relation of rheumatic fever to strep infections has become known, the disease has lost that attractive aura of mystery that still surrounds "diseases of unknown etiology," like lupus or rheumatoid arthritis. The river Nile also became less interesting once its springs were discovered.

The third problem I have been hesitant to put down, yet it is not without precedent. It is a fact that most people of influence and power are concerned about myocardial infarction if for no other reason than because it may strike *them.* But as far as rheumatic fever, they are past that age, and the children affected seem always to be someone else's; in old Boston they were Irish immigrants; in New York, Puerto Ricans; in Colorado, Hispanos; in New Mexico, Chicanos; in Arizona, Indians; and everywhere, Blacks.

Finally, the public may ask, in appropriate Madison Avenue lingo: "What have you done for me *lately?*" and the honest answer, I am afraid, is "not much," if one excludes, as outside our field, the surgical repair of rheumatic valve disease and the general progress in cardiac therapy. Telling them that new streptococcal products are being discovered or that new antibodies against them are being measured is not quite satisfactory. This, of course, is a problem that plagues most of the biomedical establishment, where many interesting discoveries have been made, but the

practical fall-out *lately* has been scanty.

As for the private life of rheumatic fever, isn't this another bit of nonsense? Not even people are entitled to a private life anymore, what with electronic snooping and central data banks, let alone diseases. Besides, what has this to do with public relations? Plenty, in fact, if the private life, as in the case of RF, can be described as disorderly at best (Table 3). Since the private life begins with family relations, let me say that there are a lot of doubts and confusions about this disease's family background. Cardiologists claim it, but only if heart disease ensues; rheumatologists are interested in its joint manifestations, but rheumatic fever only "licks" the joints; and students of infectious diseases may consider only the preceding streptococcal infection to be in their proper province. Rheumatic fever thus is a sort of multiple strep-child.

TABLE 3
Private Life of Rheumatic Fever

1. **Lack of warm family ties: relation to cardiology, rheumatology, and infectious diseases, all ambivalent and mixed-up.**
2. **Contested paternity of RHD cases.**
3. **Vital statistics hard to get.**

As if the family life of RF were not complicated enough already, the suspicion has been raised that rheumatic fever is only a putative, not a biologic, father to many cases of "rheumatic heart disease," like Joseph to Jesus. No doubt paternity used to be attributed lightly, on the flimsiest evidence. I have learned recently that until 1956 all cases of mitral regurgitation were considered rheumatic in mortality statistics, even when they were due to cardiac dilatation in hypertensive or arteriosclerotic heart disease, rather than to valvular damage. Moreover, ballooning mitral valves, calcific aortic stenosis, and perhaps the residua of viral myocarditis all may have been previously misdiagnosed as rheumatic heart disease and their proper identification is whittling away all but the genuine core of rheumatic heart disease. (What we believe at the moment is always genuine.) For this and other reasons, statistics are frightfully unreliable.

As he comes to the end of this paper, the reader will notice that I have managed so far to skirt the underlying question: are public relations worth the trouble? There are no data, as usual, to answer this important question, but it stands to reason that a disease must evoke a favorable response, interest, concern, good will, and willingness to help if its problems are to be effectively tackled. And on this positive note I'd better stop, lest I commit, on behalf of rheumatic fever, the publicrelationist's unforgiveable sin, overexposure.

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GENERAL PRACTITIONER to join 2 MD's in new Dr. Clinic adjacent to Hospital in progressive beautiful lakeside community of over 4,000; summer and winter sports. 40 bed accred. hospital. For complete details write or call Dr. G. E. Lee, 612-634-4535 or Mrs. Mary Jane Churchill, Administrator 612-634-4521 (Hospital) or 612-634-4439 Home) Glenwood, Minnesota.

(Continued on page 638)

Classified Advertisments

INTERNAL MEDICINE—IMMEDIATE OPENING—Seven Man Multi-Specialty Group has immediate need for two board qualified or certified internists. Salary commensurate with training and experience first year, full status in service corporation with incentive oriented formula thereafter. Excellent clinic and hospital facilities. Southeastern Minnesota community of 16,000, diversified economy, away from complexity of big city living. Generous benefit and time off program. Excellent educational opportunities. Contact J. D. Miller, M.D. or R. F. Lehigh, Administrator, Owatonna Clinic, P.A., Owatonna, Minnesota 55060. Call collect 507-451-1120.

VIETNAMESE PHYSICIAN—Desires employment in medically related field, Twin Cities area, while preparing for ECFMG examination. Age 37, background in general medicine. Contact Dr. Robert W. Goltz, Box 98 Mayo Building, University Hospitals, Minneapolis 55455, telephone (612) 373-8720.

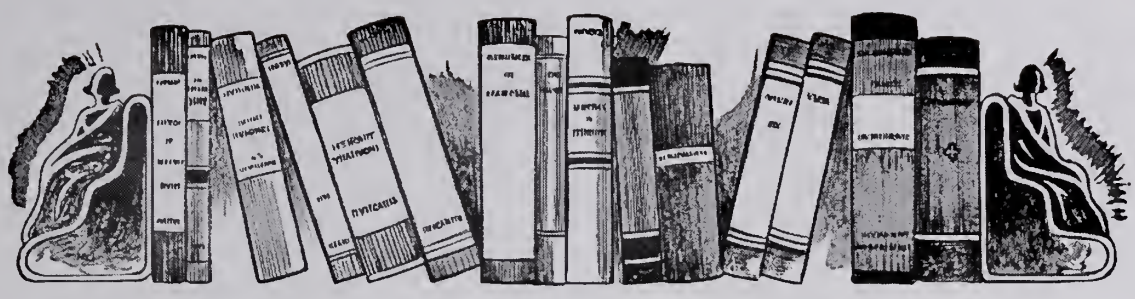
WANTED—Family Practitioner: To join busy G.P. clinic, Excellent living and practice area 20 miles from downtown Minneapolis. Generous salary and early partnership. Contact: P. J. Adams, M.D., Sundance Medical Clinic, Shakopee, Minn. (612) 445-6440.

MULTI-SPECIALTY GROUP of 24 specialists needs an Orthopedist, Family Practitioner, Internist, Pediatrician. Attractive income arrangements, association membership within 1 year, pension, extensive fringe benefits. Excellent community of 50,000. Contact: R. B. Windsor, M.D., 1011 North 8 Street, Sheboygan, WI 53081. Tel: 414/457-4461.

MSMA/MINNPAC PUBLIC AFFAIRS WORKSHOP

The Second Statewide MSMA/MINNPAC Public Affairs Workshop will be held on Saturday, September 13th at the new L'hotel Sofitel (next to the Radisson South) in Bloomington. This year's program will be highlighted by a panel discussion of malpractice and possible solutions to the problem. Panelists will include state legislators, plaintiff and defense attorneys, and representatives from MSMA, AMA and The St. Paul Companies. The workshop will also include presentations on other legislative issues and political involvement by speakers representing MSMA, MINNPAC, the Woman's Auxiliary, the AMA Board of Trustees, and campaign management professionals. Minnesota's Fourth District Congressman Joseph Karth will be the luncheon speaker. The entire Minnesota legislature will be invited to attend the session on malpractice and be guests of the MSMA and MINNPAC for the luncheon. Registration will start at 9:00 a.m. with coffee and rolls available. The meeting will begin at 9:30 and conclude at approximately 3:30 p.m.

All Minnesota physicians and their spouses interested in becoming more involved politically and better informed on malpractice and other important issues facing medicine should plan *NOW* to attend. A registration fee of $10.00 per person includes the luncheon. Checks should be made payable to MINNPAC and mailed to Metro Medical Office Bldg., Room 206, 825 So. 8th St., Minneapolis 55404. For further information you may call the MSMA office at (612) 222-6366 or MINNPAC at (612) 336-6262.



Book Reviews

HANDBOOK OF POISONING by Robert H. Dreisbach. 7th edition, Lange Medical Publications, Los Altos, California. 515 pages

This practical pocket sized book addresses itself to the practicing physicians in private or hospital practice. In a well organized approach it elicits the steps to be taken in sequence for each problem. It informs the reader of the reasons without losing itself in details of pharmacology, metabolism or chemistry.

The book covers general considerations of poisoning, a list of equipment necessary to meet practically all problems of poisoning and covers domestic, agricultural, industrial and cosmetic hazards as well as food and pharmaceutical poisoning. A small but important section deals with adverse effects of medications in pregnancy. The index is excellent and uses tradenames wherever indicated and gives instant reference in an emergency.

We find this book indispensable for office as well as emergency rooms.

Horace H. Zinneman, M.D.
Veterans Hospital

WHO'S LISTENING. Leonard A. Read. The Foundation for Economic Education, Inc., Publisher. 201 pages.

This is a compendium of a series of philosophic musings of the author, in which he deals with numerous, every day problems that enter the minds of most of us: restraint or release, sheltering ideology, the great and the celebrated, the world of exuberance, Mr. Anonymous, etc. to the extent of 30 such varied and fascinating thought.

The reader may not agree with the author in all respects, but at no time did I find myself in contempt with our differences of opinion. There were numerous opportunities for deep thoughts and meditations. I can sincerely recommend it for casual or deliberate reading.

I commend the author for very excellent editorial arrangement. Within each chapter he has pertinent subheadings that lead one to specific interest. There is, in addition, a useful index.

Carl O. Rice, M.D.
Editor Emeritus

PSYCHODRAMA, THEORY AND THERAPY, edited by Ira A. Greenberg, 486 pp., Behavioral Publications, 1974. Price: $16.95.

This is an excellent place to begin a serious exploration of psychodrama and its many ramifications. Dr. Moreno and his followers have established some concepts and procedures which are so imbedded in the psychological scene that we have forgotten their origin. Terms like "group psychotherapy," "the psychology of the here and now," "role reversal," 'sociogram," are all directly traceable to Dr. Moreno and his work. All active techniques in psychotherapy were first tried out by Dr. Moreno, and whether one perceives himself as being a Transactional Analyst, a Gestalt Therapist, or an Interactional Group Therapist his origins are directly traceable to Dr. Moreno.

This book is well written and its theoretical sections pin down some difficult concepts with a minimum of words. I particularly enjoyed the sections written by Irene Clepper describing the Theatre of Psychodrama in Minneapolis, as well as Raymond Corsini's discussion of Immediate Therapy. The contributors to this book uniformly state their views clearly.

This is a good book for both the novice and experienced psychotherapist.

James Janecek, M.D.
St. Paul, Minnesota

GENERAL PATHOLOGY, Walter, J. B., and Israel, M. S. Longman, Inc., Churchill, Livingstone, Edinburgh and London, 1974. 681 pages, price: $32.50.

This well-written book is published by Churchill, Livingstone and at first inspection a paraphase of W. Churchill is brought to mind—"I opened the book and nothing came out." Part of this feeling is due to a subject organization that is completely foreign to a U.S. medical graduate.

Tumors are disposed of in 85 pages that only minuscully cover the attributes of specific tumors from specific sites; benign and malignant tumors are treated more like one large group with common characteristics. Benign tumors receive very short shrift. By contrast, as many pages are occupied by chapters on immunity, the immune response and hypersensitivity. These chapters, as well as those on respiratory failure, renal failure and acid-base balance, tend to be heavy in physiology and yet do little justice to the complexity of the subjects.

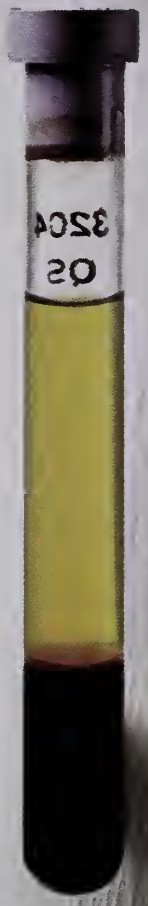
Where is the niche for this book? Perhaps it could be used for those medical students who need only a smattering of what has been considered classical pathology. Some of my non-pathology colleagues might want to use the book as bedtime reading to broaden their outlook without being burdened, to put them to sleep, and to save money (this quite expensive book would be cheaper, per night, than a paperback).

Robert Woodburn, M.D.
St. Paul, Minnesota

When serum cholesterol demands attention...

patients may need...

- Diet control
- A proven cholesterol-lowering adjunct to diet*
- Convenient once-a-day dosage*
- Reasonable cost*



*Choloxin®
(sodium dextrothyroxine)

An agent for low density lipoproteins, "type II hyperlipidemia," in euthyroid, non-cardiac patients

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Deerfield, Illinois 60015

See reverse side for full prescribing information

Choloxin® (sodium dextrothyroxine)

The Lipid-Lowering Agent with Once-A-Day Dosage

Four strengths . . . 1, 2, 4, and 6 mg. . . . are available making the scored tablet regimen a flexible dosage system. And, for most patients, CHOLOXIN tablets offer once-a-day dosage.

AN IMPORTANT NOTE:
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CHOLOXIN® (sodium dextrothyroxine) Single-Tablet-A-Day Dosage Schedules

See prescribing information in package insert reproduced below.

	Starting Dosage	Increased Monthly by	Usual Maintenance	Maximal Recommended
Adult Hypercholesterolemic	1.0-2.0 mg.	1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac	0.5-1.0 mg.	1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as D-3,5,3′,5′-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

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Deerfield, Illinois 60015



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Special Concert

The Minnesota Society for the Prevention of Blindness and the Pre-School Medical Survey of Vision and Hearing will sponsor a special concert of the Minnesota Orchestra, 8:00 P.M., October 13, Orchestra Hall, Minneapolis. The Survey is a public service organization of the Minnesota State Medical Association in conjunction with the Society.

Music director, Stanislaw Skrowsczewski will conduct the Orchestra. The concert is a memorial to Mrs. Alfred Pillsbury, charter board member and first president of the Society. Proceeds will help support MSPB and Pre-School programs including a screening survey of four-year-old children for vision and hearing deficiencies, eye disease detection screenings for adults, eye safety seminars in schools and industry, a farm eye safety education campaign, and eye safety and health education programs.

Write or call, Prevent Blindness, 375 Jackson St., St. Paul, Minnesota 55101, (612) 227-8808 for further information and tickets.

PERFORMANCE. IT'S A MATTER OF RECORD.

- an unsurpassed record validated in several thousand clinical papers
- rarely interferes with mental acuity
- wide margin of safety



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.
Contraindications: Patients with known hypersensitivity to the drug.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety and tension, 5 to 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
Supplied: Librium® (chlordiazepoxide HCl) *Capsules*, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Libritabs® (chlordiazepoxide) *Tablets*, 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable.

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Nutley, New Jersey 07110

LIBRIUM®
chlordiazepoxide HCl/Roche
5 mg, 10 mg, 25 mg capsules

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Philadelphia, Pa. 19103

IN PAINFUL ACUTE CYSTITIS*

*nonobstructed; due to susceptible organisms



RELIEVE THE PAIN

WHILE YOU ELIMINATE THE PATHOGENS.

FOR THE PAIN

☐ **Early relief of painful symptoms** such as burning and pain associated with urgency and frequency.

FOR THE PATHOGENS

☐ **Effective control of susceptible pathogens** such as *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris.*

Appropriate antibacterial therapy: Up to 3 days therapy with Azo Gantrisin 4 to 6 tablets *Stat.*, then 2 tablets *q.i.d.*; then 11 days with Gantrisin (sulfisoxazole) may be considered.

AZO GANTRISIN®

(50 mg phenazopyridine HCl and 0.5 Gm sulfisoxazole)

Before prescribing, please consult complete product information, a summary of which follows.

Indications: In adults, urinary tract infections complicated by pain (primarily cystitis, pyelitis and pyelonephritis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. *Important Note:* Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response. Add aminobenzoic acid to culture media for patients already taking sulfonamides. Increasing frequency of resistant organisms currently is a limitation of the usefulness of antibacterial agents including the sulfonamides. Blood levels should be measured in patients receiving sulfonamides for serious infections, since there may be wide variations with identical doses; 12 to 15 mg/100 ml is considered optimal for serious infections; 20 mg/100 ml should be the maximum total sulfonamide level, as adverse reactions occur more frequently above this level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period. Contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with gastrointestinal disturbances, because of phenazopyridine HCl component.

Warnings: Safe use in pregnancy has not been established. Teratogenicity potential has not been thoroughly investigated. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported; clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts and urinalysis with careful microscopic examination should be performed frequently during sulfonamide therapy.

Precautions: Use with caution in patients with impaired renal or hepatic function, severe allergy, bronchial asthma and in glucose-6-phosphate dehydrogenase-deficient individuals. In the latter, hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme (Stevens-Johnson syndrome), skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis. *C.N.S. reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, polyarteritis nodosa and L.E. phenomenon. Du to certain chemical similarities with some goitr gens, diuretics (acetazolamide and thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter productio diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Usual adult dosage for acute, painfu phase of urinary tract infections is 4 to 6 table initially, then 2 tablets four times daily for up t 3 days. If pain persists, causes other than infe tion should be sought. After relief of pain has been obtained, continued treatment of the infe tion with Gantrisin (sulfisoxazole) may be con sidered.

Note: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine soon after ingestion.

How Supplied: Tablets, each containing 0.5 sulfisoxazole and 50 mg phenazopyridine HC —bottles of 100 and 500.

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COLLEGE OF PHYSICIANS

STATE MEDICAL ASSOCIATION

minnesota medicine



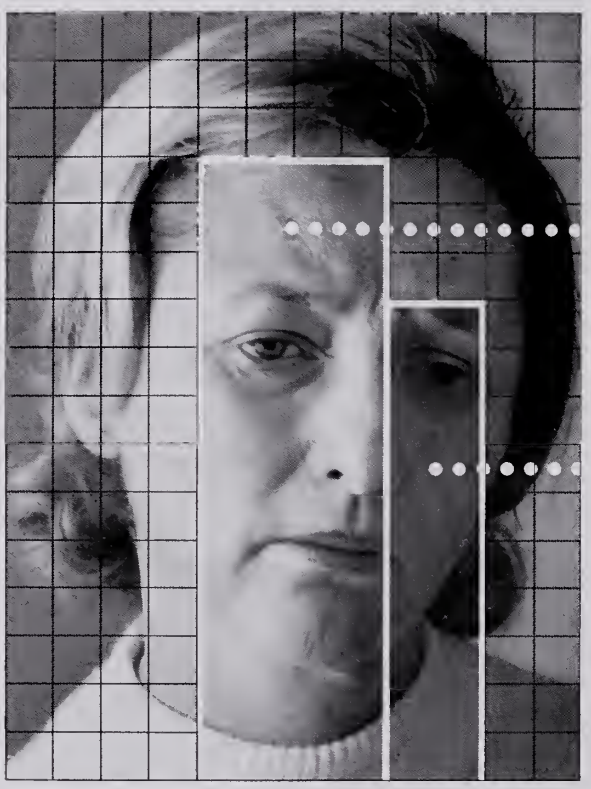
nnesota 'Medicine' "

H. G. Rice, M.D.

SEPTEMBER, 1975

V.58 #9

Both often



Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequenc and/or severity of grand mal seizures ma require increased dosage of standard ant convulsant medication; abrupt withdraw may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) hav occurred following abrupt discontinuanc (convulsions, tremor, abdominal and mu cle cramps, vomiting and sweating). Kee addiction-prone individuals under carefu

respond to one

According to her major ymptoms, she is a psychoneu- otic patient with severe nxiety. But according to the lescription she gives of her eelings, part of the problem nay sound like depression. This is because her problem, lthough primarily one of ex- essive anxiety, is often accom- anied by depressive symptom- tology. Valium (diazepam) an provide relief for both—as he excessive anxiety is re- eved, the depressive symp- oms associated with it are also ften relieved.

There are other advan- ages in using Valium for the nanagement of psychoneu- otic anxiety with secondary epressive symptoms: the sychotherapeutic effect of alium is pronounced and apid. This means that im- rovement is usually apparent in the patient within a few days rather than in a week or two, although it may take longer in some patients. In addition, Valium (diazepam) is generally well tolerated; as with most CNS-acting agents, caution patients against hazardous occupations requiring complete mental alertness.

Also, because the psychoneurotic patient's symptoms are often intensified at bedtime, Valium can offer an additional benefit. An *h.s.* dose added to the *b.i.d.* or *t.i.d.* treatment regimen can relieve the excessive anxiety and associated depressive symptoms and thus encourage a more restful night's sleep.



Valium® (diazepam)

2-mg, 5-mg, 10-mg tablets

in psychoneurotic anxiety states with associated depressive symptoms

surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

Precautions: If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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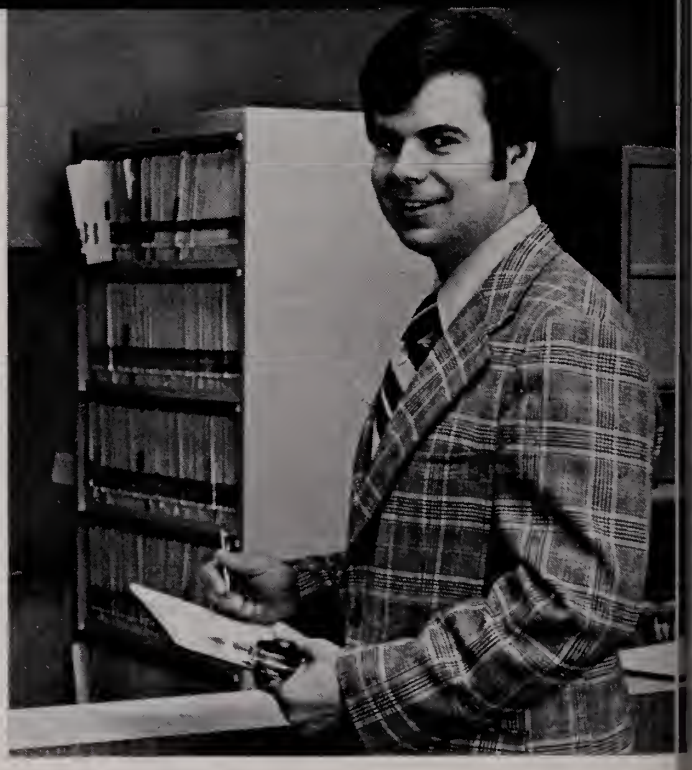
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Editor's Notebook

THE OTHER SIDE OF THE COIN

Many readers have said they liked what I wrote in my April editorial: "On Shortening Manuscripts." But how, asked one, did I become such an authority on brevity? Well, that's a long story. Back in the dark ages of my prosaic career, about 1966, I was attending a week's course on medical writing given in Chicago by the *Journal of the American Medical Association.* As I was wading through examples of muddy medical prose, this thought flashed through my cortex: If all medical writing has to be so long, why not develop a set of sensible rules for making long articles publishable? From that hot flash came this article, which the Editor of the *Journal of the American Medical Association* is graciously allowing me to republish now.

Space-Occupying Gambits for Medical Writers*

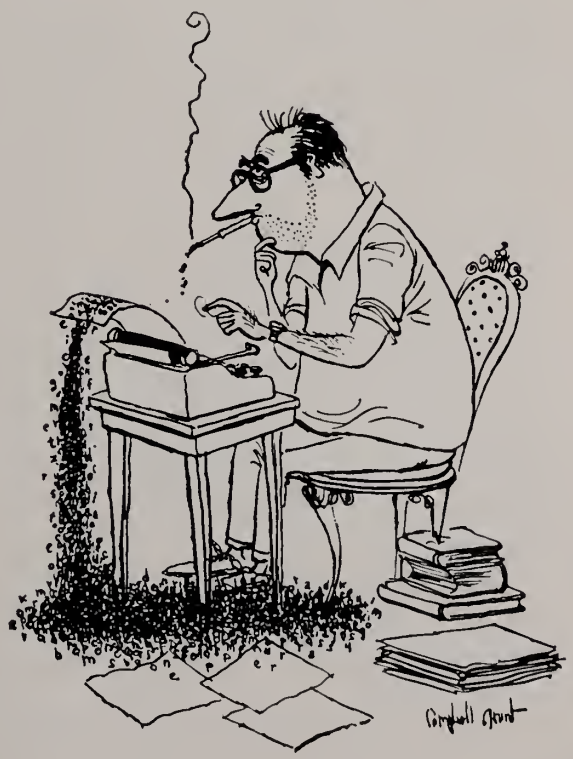
As a rule, disease as it stalks through the land cannot keep pace with the incurable vice of scribbling about it.—John Mayow, de Rachitide, *1668*

SPACE-OCCUPYING PROSE diffuses through medical writing like a fog. Yet the space-consuming efforts of many of us continue to be rejected. The message of this essay is that obscurity, when properly inflated, can lead to publication. Your goal is clear—to produce the greatest number of papers from the minimal amount of data using the maximal number of words.

Before I describe the basic gambits, I will tell you how you should approach the game. Say nothing well and don't stop when you have said it. Remember that clarity is degrading, that blunt statements are impolite, and that vagueness is safer than precision. Be aloof. Aloofness implies dignity, and dignity is a flexible weapon in the fight against clarity. If you want to become an artful practitioner of turgid but publishable prose, master the following ten gambits.

The Windfoggery Weave

Windfoggery is the bedrock of all obscurity. Wind and fog do not coexist in nature but can be woven together on the printed page. Give the reader a low-fact diet with a high-jargon content. Sprinkle with polysyllabic words and scramble the syntax. For example, if you doubt a predecessor's methods, don't say: "Jones' methods are questionable." Raise the fog index and the wind



Reprinted from my article in JAMA, 200:1, April 3, 1967 by permission.

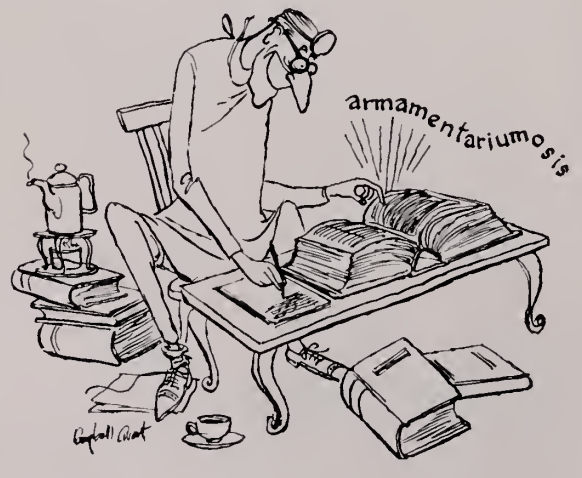
velocity by saying: "The quantitative variables assayed by Jones were analyzed and appeared, according to our interpretations, to demonstrate significant fluctuations which seemed to vacillate diurnally." Note the murky merging of wind and fog.

The Retrospective Ramble

In the retrospective ramble, pay homage to the past by exhaustively reviewing your subject. The flood of references will inundate the editor and drown the reader. Refer to inaccessible, outdated, or foreign journals. This adroit maneuver discourages or diverts critics. Their futile search through back alleys of print will wear down objectivity and blur perspective. Complete your conquest over comprehension by quoting everything (or nearly everything) that has been said about your subject. Whether the material is relevant is not important; it is the number of references that count. But it is wise to be discreetly excessive. The discerning editor will quickly reject such a clumsy effort as this: "I[26,31,14] believe that[21,88] this technique[25,85,99] of using excessive references[922] to previous papers is abused[71,93,502] by most authors,[28,192,617] particularly myself[1,22,35,81,629] in my extensive review of articles,[67,84] most of which have been rejected by numerous journals before acceptance."[0]

The Humble Hedge

The humble hedge is a gambit whereby you qualify your meaning into nothingness while appearing to be objective. Always convey doubts about your statements. Arrange a retreat from clarity with hedge verbs like *indicate, suggest, appear, may,* and *might.* Withdraw with these nouns: *speculation, conjecture, theory,* and *hypothesis.* Hedges can be classified as first, second, and third order or as single, double, and triple barrelled. A fourth-order or quadribarrelled hedge is clumsy and should be avoided. A fifth-order hedge, such as "Speculation about etiological factors might possibly suggest that previous investigators may have been wrong," is excessive and poor form. The sentence could be reduced to a third-order hedge with only slight loss of ambiguity.



The Passive Ploy

In the passive ploy, place yourself in the background and emphasize vague pronouns, dry facts, and lofty concepts. To do this, write in the passive voice. You can add words, befog your meaning, and become a dispassionate authority. *It was discovered by the author* is nearly 4½ times longer than *I found* and is more humble. *It was reported by this investigator in a recent communication* requires eight times more space than *I noted* and is more sedate. But how, you may ask, can I be sure I am writing in the passive voice? You could consult books of grammar, but most doctors are too busy for that sort of thing. So I have gathered together some practical suggestions: commence your sentences with impersonal remarks—*it is thought, it is felt, it is believed;* strip your sentences of verbs which picture or imply action and glue your ideas together with *have, seem,* or some form of *to be;* delete the personal pronouns—*I* or *we*—whenever they appear; and strew your sentences with *whichs, ofs,* and *bys.* The passive voice allows you to avoid definite statements, and, of course, the true scientist is never blunt. Use the passive ploy often. It is the most powerful space-eating weapon at your command.

The Word Wedge

Word wedging is the art of forcing impressive words into sentences where they don't belong. The careful wedger selects his tools meticulously. He prefers abstract terms with scientific overtones, eg, *armamentarium, congeners, continuum, dynamic, esoteric, kinetics, methodology, modality, oncogenesis, parameter,* and *sophisticated.* The following example of wedging is from an article in a well-known medical journal: "Substances which are immunologically foreign are composed of autochthonous materials; these are not diagnostic, but

with progressive increase as seen by serial samples, in association with other suspicious parameters, the electrophoretic pattern may become significant as a predictor." Observe the passive mingling of windfoggery, hedging, and wedging—all combining to produce a hieroglyphic obfuscuity.

The "That" Thrust

Put this gambit into play by thrusting the word "that" into the start of your sentences. With "that," you can introduce your sentences, qualify your thoughts, blunt your meaning, express wonderment, and consume space. Let me illustrate with some examples: "It is fascinating to note that . . . In spite of the fact that . . . It is often the case that . . . But it may be possible that . . . There can be little doubt that . . . It is interesting to observe that . . ." Notice the running start. Each example consists of six obstacles the reader must run through before he reaches the beginning of the sentence. Think of "that" as a suitcase word. Whenever you use it, you carry along verbal baggage, and, that, after all, is your mission.

The Verb Void

Save this gambit for your first revision (a second revision is rarely necessary in space-occupying writing). Read over your paper and look for verbs which can be changed into nouns. Then void your sentences of vulnerable verbs and rearrange the entire sentence. Study these examples to see how the gambit works.

Before Revision	After Revision
Then we *decided* to *explore* the other *possibility*. (8 words)	Then the *decision* was arrived at that an *exploration* of the other possibility was deemed advisable. (16 words, 100% increase)
We *investigated* what *causes* cells to *mutate*. (7 words)	We then made an *investigation* of what the *causes* were for the *mutation* of the cells. (16 words, 130% increase)
Surgeons *enlarge* the cavity by *incising* laterally. (7 words)	The best means for the *enlargement* of the cavity by surgeons is by means of a lateral *incision*. (18 words, 160% increase)

As a beginning gamesman, you are no doubt impressed most by the increase in the number of words. With experience, you will realize another virtue of the verb void—it breeds other gambits. In the example above, the passive ploy and the "that" thrust come into play. Finally, the act of trading lean, active verbs for edematous, sedentary nouns is always good gamesmanship.

The Double Dawdle

The double dawdle permits the gamesman to double his word volume while keeping his facts constant. This gambit has two variations—the supersuperlative dawdle and the redundant dawdle. Execute the supersuperlative dawdle by adding the words *very, markedly, much,* and *quite* to your adjectives. For example, if you are describing a big uterus, you can call it a *very* enlarged uterus, a *markedly* enlarged uterus, a *quite* enlarged uterus, or a *much* enlarged uterus. Beware of the triple or multiple dawdle. A *very markedly enlarged uterus* is not likely to slip through the editor's net. Only the reader and you will appreciate the profundity of your distinction. Perform the redundant dawdle by joining together such words as *equal halves, hazardous risks, linear lines,* and *tumor mass.* You appear to be reinforcing your meaning, but you are really just duplicating words.

The Paragraph Parry

When you have a large space to fill, word gambits are good, but paragraph parries are better. Open your paragraph by sallying forth with a decisive sentence. The reader, caught off guard, will plunge into the paragraph. Immediately parry with a series of indecisive sentences. What you give away in your opening, take back in the discussion. Begin with courage and end with prudence—no more can be asked from a dignified scientist. Here is an example of a paragraph parry.

"I define cerebral palsy as any paralysis, weakness, incoordination, or dysfunction resulting from brain damage. Jones, however, regards cerebral palsy as any condition characterized by paralysis, weakness, incoordination, or other derangement of motor function due to pathology of motor control centers of the cerebral cortex. On the other hand, Smith's definition is more comprehensive: '. . . a condition occurring from birth trauma and resulting from interference with the motor system and leading to neuromotor dysfunction, psychological aberration, atypical convulsions, and behavior disturbance of organic origin.' It is obvious that the brain is a complex organ subject to varying de-



grees of damage which are manifest in unusual disturbances interpreted in various fashions by different, independent observers."

The writer's opening sortie is a crisp definition. He then counters with two meandering redefinitions, and completes the gambit by admitting hopeless confusion.

Finishing Finesse

Employ the finishing finesse in the backwaters of the discussion and in the stagnant summary. Only the able gamesman should handle this gambit, for he must manipulate ideas which were never expressed. The finishing finesse may be defined as the use of large words in loose phrases near the end of a long paper to achieve a wandering ending, eg, "The pathogenesis of the diverse forces operative in electrolyte disturbances were studied, and it was concluded that the variability of the methodology did not permit delineation of the therapeutic modalities." Observe that the writer concludes by hovering above the level of concrete, and the reader ends where he started—fogbound.

Richard L Reece MD

P.S. On page 677 you will find a questionnaire. If you have 30 seconds to spare, we would appreciate your filling in this questionnaire and returning it to us.

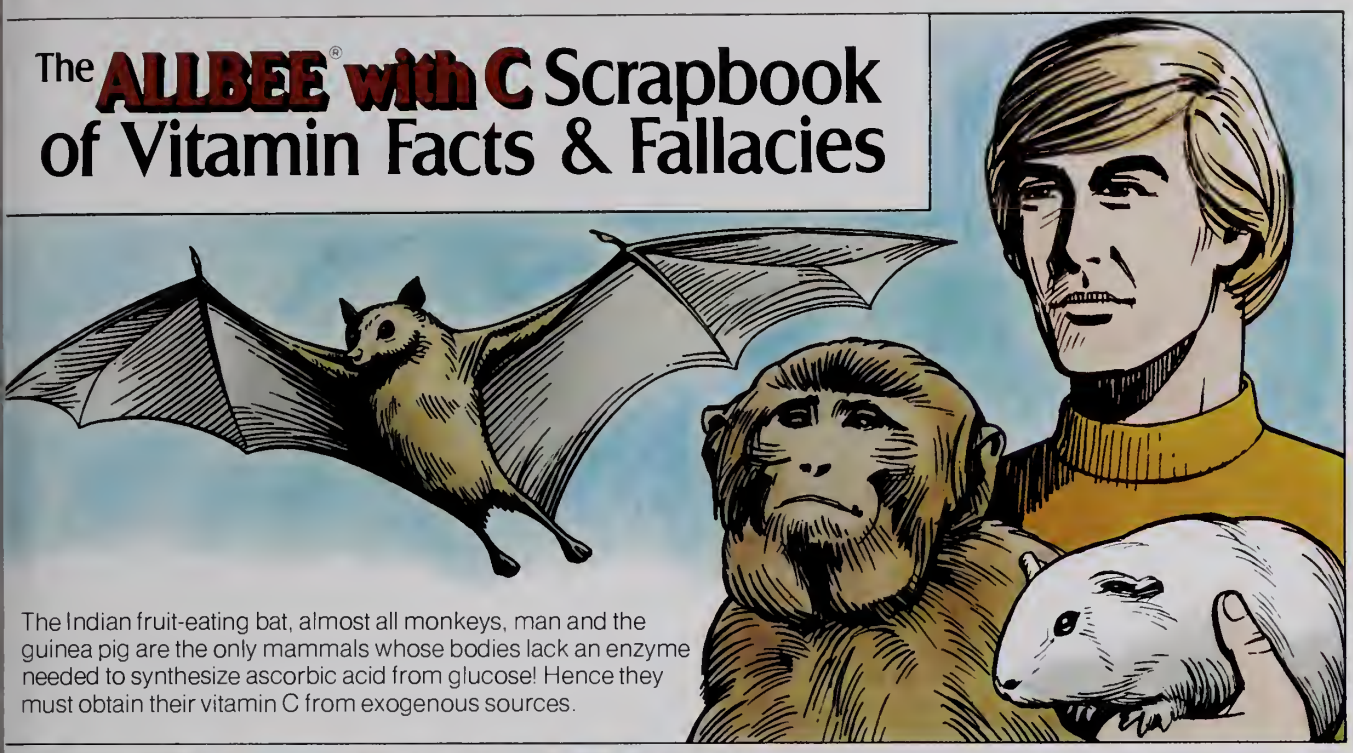
Special Concert

The Minnesota Society for the Prevention of Blindness and the Pre-School Medical Survey of Vision and Hearing will sponsor a special concert of the Minnesota Orchestra, 8:00 P.M., October 13, Orchestra Hall, Minneapolis. The survey is a public service organization of the Minnesota State Medical Association in conjunction with the Society.

Stanislaw Skrowsczewski, music director, will conduct the Orchestra. The concert is a memorial to Mrs. Alfred Pillsbury, charter board member and first president of the Society. Proceeds will help support MSPB and Pre-School programs including a screening survey of four-year-old children for vision and hearing deficiencies, eye disease detection screenings for adults, eye safety seminars in schools and industry, a farm eye safety education campaign, and eye safety and health education programs.

Write or call, Prevent Blindness, 375 Jackson St., St. Paul, Minnesota 55101, (612) 227-8808 for further information and tickets.

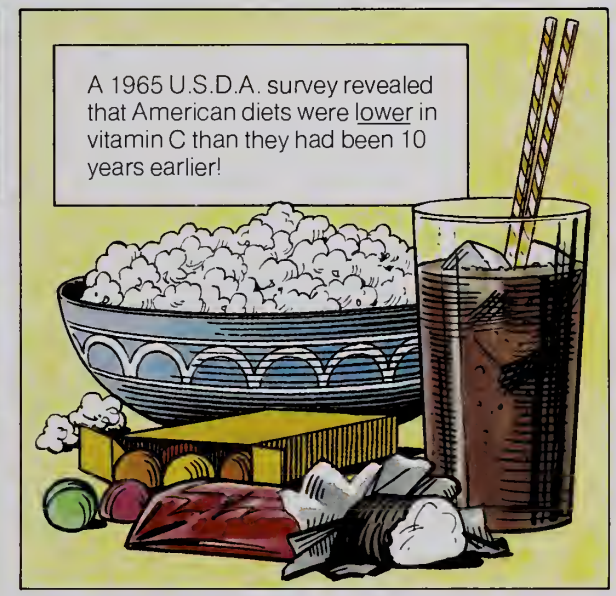
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President's Letter



Frustration

In May 1975 Mid-Continent Surveys Inc. conducted a personal interview survey of representative cross-sections of 998 Minnesota adults, including 512 in the Twin City area, for the Minnesota Hospital Association, the Minnesota State Medical Association, and the Minnesota Blue Cross-Blue Shield. The survey questions covered health care quality, costs, and accessibility. The results of this survey must be almost incredible and truly amazing to those who have accepted the position of the news media and many politicians that there is a major problem and general public concern about health care quality and accessibility. For example, in this survey 76 per cent feel the health care they receive is good or very good; 15 per cent say it's all right; and only six per cent feel it is poor or very poor—only five per cent say they have problems getting health care! Generally, sex, age, income, education, and residence did not make a significant difference in response.

Certainly the results of this survey must be considered as an important news release and warrants editorial comment. Certainly the survey results should be of great interest to every citizen of Minnesota and particularly to our legislators, our congressmen and their legislative assistants, economic technicians, and the host of non-medical advisers on health matters. Certainly the news media will give the survey the exposure and prominence it deserves.

But, what has happened? On July 1, 1975 Mid-Continent Surveys released the results of this survey to the news media. The metropolitan and some non-metropolitan newspapers carried this news article, but "buried" it in the inside pages under headings such as "Health Care Rates 'High'—Like the Cost, State Survey Shows" and "Minnesota Health Care Satisfactory." One of the largest metropolitan newspapers devoted only *17* lines to the report! Few, if any, of the television news programs even mentioned the survey. There has been no editorial comment. I doubt that more than a handful of those who should know the detailed results of the survey even know the survey was done.

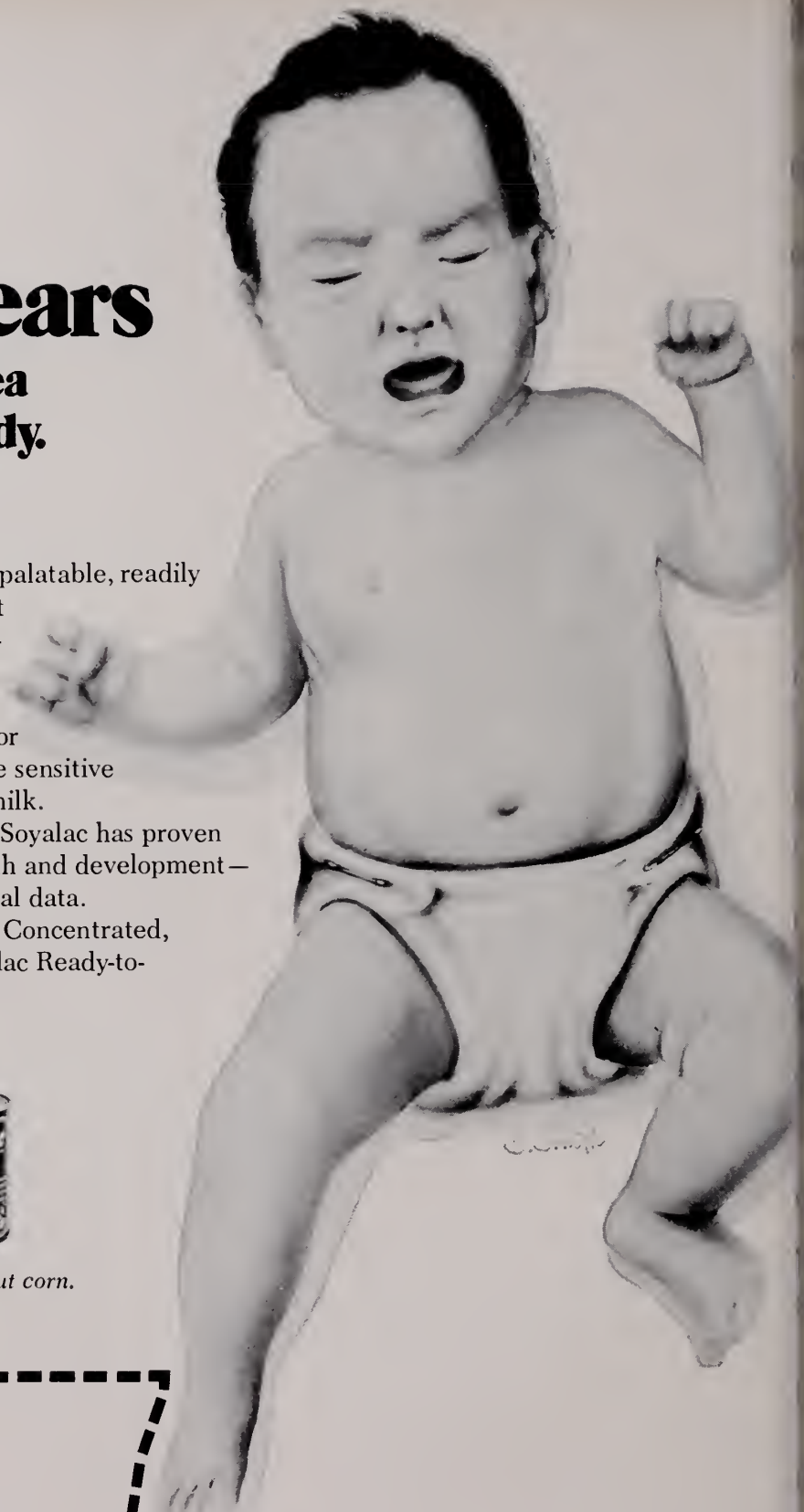
I feel frustrated! How can this information be widely circulated and reported and given the attention it deserves? It is news and important news. What would a similar national survey show? Important programs and legislation with great impact and potentially damaging effects on our economy and health care system have been recently and are about to be enacted on the basis of misinformation if the results of this survey are similar throughout the country.

Perhaps the survey and its results should be challenged. It would be preferable to being ignored. I feel frustrated. What is your remedy?

G. Roy Diessner, M.D.
President
Minnesota State Medical Association

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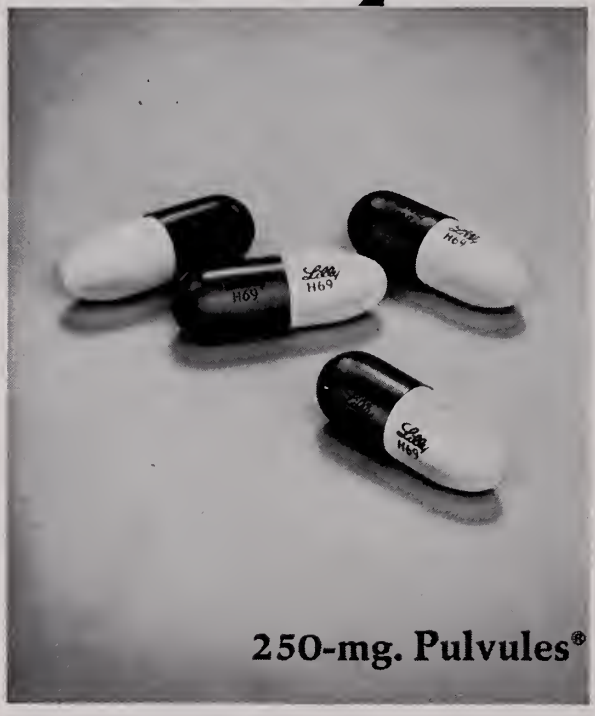
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Management of Acne Vulgaris with Antibiotics

Twenty-Two Years' Experience

FREDERIC T. BECKER, M.D.*

Since 1952 I have used tetracycline in the management of acne. Evaluation in 1974 of 22 years' experience with this therapy indicates that 101 patients (aged 15-62 years) received this treatment for periods varying from eight months to seven years. Tetracycline (0.5 to 1.5 gms. daily) was highly effective and well tolerated in the management of nodular and cystic acne in 62 of the 101 patients. Thirty-nine of the 101 patients experienced a relapse while on this therapy. Cultures of the pustule content in these patients demonstrated organisms resistant to tetracycline but sensitive to erythromycin, chloramphenicol, minocycline (98% of the organisms) and clindamycin (90%). In these 39 patients, three months of minocycline (100 mg. twice a day) therapy produced improvement in 32 patients; recrudescence occurred in the other seven patients.

In 1951 Andrews et al.[1] reported favorable results in the management of acne vulgaris with antibiotic therapy. Subsequently Noojin et al.,[2] Robinson,[3] Belasario[4] and Hurst[5] substantiated Andrews' findings. In 1952 I initiated a study of the therapeutic management of comedone, cystic, pustular or nodular acne with various antibiotics. After three years of this study, I[6] concluded that tetracycline hydrochloride was the most beneficial antibiotic, but I believed that its bacteriostatic action was probably only incidental. The explanation for this observation awaited the later work of Strauss and Pochi,[7] who showed that these antibiotics exerted a lipolytic effect on the sebaceous glands, thus reducing the production of unsaturated fatty acids and resulting in a reduction in inflammation.

At this writing, now some 22 years into my studies of antibiotic therapy in acne vulgaris, two major questions arise:

1. Does the prolonged use of tetracycline result in adverse reactions? If so, what are these reactions?
2. With the prolonged use of tetracycline, what bacterial resistance may develop?

To answer these questions, an analysis of the data accumulated on my patients treated with tetracycline was undertaken. 101 patients, varying in age from 15 through 62 years, constituted the study group. The predominating age range was that from 16 through 22 years. All of the patients in this study had been on a dosage schedule of tetracycline varying from 0.5 grams to 1.5 grams per day for treatment periods ranging from eight months to seven years.

To secure adequate data for the study, each patient had a general physical examination in 1973 and laboratory studies (blood analysis by the Technicon SMA-12/60 channel auto analyzer, hemoglobin determination, hematocrit measurement, white blood cell count, differential white cell count and urinalysis) were done at this time. Adverse reactions, when present, were evaluated. The results of this analysis of our data showed:

Hematologic Analysis

Computer analysis test results were normal except for the occurrence of an elevated bilirubin in two patients. One of these two patients had congenital bilirubin elevation, and the other was in

*Department of Dermatology, The Duluth Clinic, Ltd., Duluth, Minnesota and Assistant Clinical Professor, University of Minnesota School of Medicine.

Presented at AMA Scientific Assembly, Section on Dermatology, Chicago, Illinois, June 24, 1974.

the recovery phase of hepatitis—and he was subsequently able to continue on his antibiotic regimen (minocycline 100 mg./day) without adversely affecting his test results on a hepatic profile study.

All hemoglobin levels were excellent, lying in the range between 12 and 15 grams. White blood cell counts and differential white cell counts were all normal.

Urine Studies

These were all normal.

Physical Examination

Results showed no change from pretetracycline treatment status.

Gastric Intolerance

This was mild and only occasional patients reported this complication. This symptom was usually relieved when the paticnt was re-instructed in the proper administration of the medicine. (The importance of taking the tetracycline when the stomach was empty—and the necessity of taking it with water—were stressed. It was explained to the patients that magnesium and calcium ions block absorption of the medication, hence food —especially milk—must not be taken for one-half hour before and for one-half hour after taking the medicine).

Yeast Infections

Only three percent of the female patients developed yeast infections; topical antifungal agents readily controlled this.

Urticaria and Aphthous Ulcers

One of this study group was alleged to have urticaria due to the tetracycline; on minocycline therapy this patient improved without further untoward symptoms. Another of these patients had aphthous ulcers due to tetracycline therapy, and changing to clindamycin produced improvement without adverse reactions.

Antibiotic Resistance

The acne pustule contents of those patients who had failed to respond to tetracycline therapy or who had relapsed while on this treatment were cultured and sensitivity tests to multiple antibiotics were carried out. Sensitivity test discs indicated that the organisms of 39 percent of the 101 patients had developed a resistance to tetracycline. Most of these organisms, however, were highly sensitive to erythromycin, chloramphenicol, minocycline and clindamycin; 98 percent of the resistant group had organisms sensitive to minocycline; resistance to minocycline was shown only by several species of enterobacter; 90 percent of the resistant group had organisms sensitive to clindamycin.

Of the 39 patients who had tetracycline-resistant organisms, 90 percent showed Staphylococcus epidermis. These 39 patients were treated with minocycline 100 mg. twice a day for a minimum period of three months; 32 improved, seven had recurrent flare-ups of their acne.

My experience has shown, however, that cultures and sensitivity studies are rewarding in the academic sense, from a practical standpoint, doubling the dose of tetracycline, or, if this fails, switching to another antibiotic has proved just as satisfactory and much less time consuming and expensive.

Conclusion

I found during the 22 years of this study that tetracycline (0.5 gm. to 1.5 gm daily) constituted very effective management for most cases of nodular, cystic or pustular acne vulgaris. In the age group treated (15 through 62 years), it was well tolerated; additionally, it was inexpensive.

Adverse reactions *were* experienced by patients on long-term tetracycline therapy. These reactions included gastric intolerance, yeast infections, urticaria, aphthous ulcers and antibiotic resistance. Aside from the latter, however, none proved either frequent or troublesome. Laboratory studies of blood and urine and physical examination results showed either normal findings or abnormalities explainable on a basis other than the administration of tetracycline on a long-term schedule.

Unfortunately more than a third of the patients appeared to have organisms which were resistant to tetracycline, as demonstrated by the cultural studies. Most of the patients with tetracycline-resistant organisms showed improvement with the administration of minocycline 100 mg. twice a day.

Seven of the patients who were changed to minocycline therapy, and maintained on it for

three months, were returned to tetracycline medication, using 1-2 gm. amounts daily, in divided doses, as recommended by Baer et al.[8] Excellent responses were obtained by five of these patients; the other two patients continued to show the periodic exacerbations which they had exhibited with antibiotics given previously.

This 22-year study thus points up the effectiveness of tetracycline therapy for a large number of patients having nodular, cystic or pustular acne vulgaris, shows that few adverse reactions occur (except for antibiotic resistance), and that when they do, they are mild and easily alleviated. The study emphasizes that the most significant adverse reaction is that of bacterial resistance for which one must remain alert and either double the dose of tetracycline or substitute another antibiotic.

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Southern Minnesota Medical Association Meeting
September 27 - Holiday Inn, Mankato

Morning Session

Alternatives to Management of Varicose Veins—Karl A. Lofgren, M.D.

Gallsone Ileus—Case Report and Movie—Mansur Taufic, M.D.

Results of Surgical Therapy for Toxic Megacolon in Inflammatory Bowel Disease—Carl E. Christenson, M.D.; Stanley M. Goldberg, M.D.; Emmanuel G. Balcos, M.D.; Jerry L. Schottler, M.D.; Santhat Nivatvongs, M.D.

Depression after age of 60—Treatment and Progress—William S. Chalgren, M.D.

Clinical Experience with the Intra-Aortic Baloon Pump—Richard C. Lillehei, M.D.

Diagnosis and Management of Acute Respiratory Failure—William W. Douglas, M.D.

Afternoon Session

Use and Abuse of Inhalation Therapy—Eugene R. Lucier, M.D.

Nontraumatic Removal of Foreign Bodies from the Nose and Ears of Infants and Children—Richard P. Virnig, M.D.

A Critical Analysis of the Open Treatment of Olecranon Fractures—Elmer Lippman, M.D.

Case Report: Hyperparathyroidism with Zollinger-Ellison Syndrome—D. K. Ohrt, M.D.

Hypercalcemia Associated with Weight Loss and Right Hip and Leg Pain: A Diagnostic Dilemma—Don A. Scholz, M.D.

New Concepts of the Syndrome of Biliary Cirrhosis—E. R. Dixon, M.D.

A Simple Repair of Vesicovaginal Fistula—Michael Howard, M.D.

Panel: Alcoholism: Early Recognition and Management—Dr. Robert Morse, Director of Alcoholism and Drug Dependency Unit, Mayo Clinic Rochester Methodist Hosp.; Mr. Raymond Island, Head Councilor, Alcoholism and Drug Dependency Unit, Rochester Methodist Hospital; Dr. Thomas Briggs, Medical Director, Alcoholism Treatment Program, St. John's Hospital, St. Paul.

Evening Session

Remarks—Grant R. Diessner, M.D., President of the Minnesota State Medical Association

Remarks—Harold W. Brunn, Executive Secretary of the Minnesota State Medical Association

Remarks—Charles F. Barbarisi, M.D., President of the Southern Minnesota Medical Assso-ciation.

Address—Lyle A. French, M.D., Vice President for Health Sciences, University of Minnesota School of Medicine.

Contact: Ethel A. McClane, 1726 North Fourth Street, Mankato 56001.

Myelomeningocele in Minnesota

Incidence and Fate

JULIUS O. ESHO, M.D.* ALEXANDER S. CASS, M.D.† and PETER F. BRIGGS, Ph.D.‡

The incidence of myelomeningocele in Minnesota from 1966 to 1970 was 0.6 per 1,000 live births. The sex distribution was 1.5 females to one male. A follow-up of the 193 cases to mid 1974 revealed 100 dead and 93 alive. Fifty percent of the dead children died within the first 30 days of birth and the main cause of death was congenital anomaly. Sixty-six per cent of the survivors had severe physical involvement from the myelomeningocele and 2.6 surgical procedures per child. The development of criteria for the treatment of myelomeningocele in the newborn has major importance.

MOST REPORTED STUDIES on myelomeningocele have consisted of patients referred to a large medical center. Very early deaths of myelomeningocele children in outlying hospitals are not included. Therefore, there is some degree of selection in the cases reported in these studies. A significant contribution would be made if all patients born with this deformity were followed to evaluate the survival rate, the factors which influenced survival and the causes of death. Such an evaluation in unselected cases has been made in this report.

Material and Method

The mandatory birth certificates in the State of Minnesota have been examined for the five year period of 1966 to 1970. These certificates include supplemental data on birth defects. All children born with myelomeningocele during this period have been followed. The death certificate of any child who died has been examined. The parents of dead and living children were interviewed by telephone or personal contact to evaluate the type of medical treatment these children had received from time of birth.

Gillette Children's Hospital, St. Paul, Minnesota.
*Department of Urology, St. Paul Ramsey Hospital, St. Paul, Minnesota.
†Chief, Department of Urology, St. Paul Ramsey Hospital, St. Paul, Minnesota.
‡Department of Physical Medicine and Rehabitation, University of Minnesota, Minneapolis.
Supported by the Medical Education and Research Account, Gillette Children's Hospital.

Results

Incidence

The incidence of myelomeningocele in children born in Minnesota between 1966 to 1970 was 0.6 per 1,000 live births. There were 205 children born with spina bifida as listed in the Central Birth Registry. Review of the birth certificates and followup of all cases where the defect was classified as unnoticeable lead to exclusion of 12 cases; encephalocele two, subcutaneous tissue malformation one, no defect two; dermal phenomenon (sinus, discoloration, "opening") three and lipomeningocele four. The remaining 193 myelomeningocele children had a sex distribution of 1.5 females to one male.

Follow-Up

All the patients have been followed for a minimum of three and a half years and a maximum of seven and a half years. One hundred patients died and 93 are known to be living and were followed-up.

Cause of Death

Of the 100 dead children, 50 (50%) died within the first 30 days of birth (Table). The predominant causes of death in these 50 children were listed as other congenital anomalies and/or severe myelomeningocele in 28 (56%) and meningitis in 11 (22%). Of these 50 children seven had had surgical procedures (six backs closed

and one shunt).

Fifty children (50%) died after one month of age. The predominant causes of death in these 50 were listed as hydrocephalus in 17 (34%), other congenital anomalies and/or severe myelomeningocele in 12 (24%) and other causes (pneumonia, post operative etc.) in 14 (28%). In these 50 children 32 surgical procedures had been performed (17 backs closed, 11 shunts and four urinary diversions).

The most common causes of death were listed as other congenital anomalies and/or severe myelomeningocele in 40%, hydrocephalus in 22% and meningitis in 18%.

Surviving Children

There were 93 known living patients. Follow-up details were obtained in all cases according to the degree of physical involvement and frequency of back closure and shunt procedures. Family interviews were carried out in 78 cases and follow-up details were obtained according to degree of physical involvement and frequency of ileac diversions, orthopedic and other surgical procedures. Nine children were not living at home, five were lost to follow-up and one refused interview.

1. Unnoticeable Deficit: Children with no noticeable orthopedic defect. There were seven children in this group and seven surgical procedures had been performed (seven backs closed).
2. Moderate Involvement: Children who are ambulatory with the aid of appliances. There were 25 children in this group and 40 surgical procedures had been performed (23 backs closed, 11 shunts, two urinary diversions, three orthopedic procedures and one other).
3. Severe Involvement: Non-ambulatory with extensive orthopedic limitations and no expectation of ambulation. There were 61 children in this group and 161 surgical procedures had been performed (55 backs closed, 50 shunts, 29 urinary diversions and 27 orthopedic procedures).

Discussion

In Minnesota from 1966 to 1970 the incidence of myelomeningocele was 0.6 per 1,000 live births. The reported incidence of myelomeningocele is one to four per 1,000 births.[1] Some of the largest series have come from England where the population is quite stable. In Birmingham, an incidence of 2.3 per 1,000 births was found in a study covering 1936 to 1945.[2] In 1960 a congenital abnormality registry was established in Liverpool and an incidence of three myelomeningoceles per 1,000 births was reported.[3]

It would appear that in the United States the incidence is not as high as in the British Isles. In South Carolina, Alter[4] found a rate of 1.0 per 1,000 births between 1946 and 1955. The incidence was 2.5 times higher in whites than in blacks. Schwidde[5] recorded an incidence of 1.5

TABLE
Age and Cause of Death in Myelomeningocele Children and Surgical Procedures Performed

Age		Other Cong. Anom. ± Severe Myelo.	Hydrocephalus	Meningitis	Other	Total σ A
0-24 Hours	Number of Children	11#	1	0	1	13
	Back Closed	0	N.K.	—	0	0
	Shunt	0	N.K.	—	0	0
1-30 Days	Number of Children	17°	4	11+	5	37
	Back Closed	1	0	2	3	6
	Shunt	1	0	0	0	1
1-12 Months	Number of Children	11Δ	13•	6	7	37
	Back Closed	4	2	1	2	9
	Shunt	3	1	0	2	6
Over 1 Year	Number of Children	1	4	1	7	13
	Back Closed	0	2	1	5	8
	Shunt	0	2	1	2	5
	Urinary Diversion	0	1*	1	2	4*
	Total Children	40	22	18	20	100

=Surgery Not Known—1
+Surgery Not Known—1
°Surgery Not Known—1
ΔSpontaneous Back Closure—1
•Attempt to Shunt Failed—1
*Suprapubic Cystostomy—1

per 1,000 births at the University of Iowa Hospitals. For the entire State of Iowa the rate was 0.87 per 1,000.

The reported figures suggest that females are more susceptible to this condition than males. Laurence[6] reported a female to male ratio of 1.4 to one as opposed to the preponderance of males in all births of England and Wales. The series of Schwidde contained 61.8 percent females and 38.2 percent males. The sex distribution in our series was 1.5 to one.

A striking difference between the dead and surviving groups was the number of surgical procedures performed. With deaths under one month of age, due mainly to congenital lesions incompatible with life, there were seven surgical procedures in 50 children (0.1 procedures/child). With deaths over one month of age, there were 32 surgical procedures in 50 children (0.6 procedures/child). In the 93 survivors, there were 208 surgical procedures (2.2 procedures/child).

Two considerations arise from this comparison: (a) Was the surgery responsible for survival?, (b) If so, what is the quality of survival? A comparison of the 0.6 procedures/child in deaths over one month of age to the 2.2 procedures/child in the survivors infers that surgical intervention increases survival. A similar inference can be drawn from the 55 children with myelomeningocele not referred for treatment and they all died within six months.[7]

The quality of survival is an important consideration. In our 93 survivors 66% had severe physical involvement resulting in non-ambulation. A key factor in this quality of survival is the mental capacity of these children and this will be reported later.

While surgical intervention appears to increase survival, the number of surgical procedures increased with the degree of physical involvement caused by the myelomeningocele. There were 1.0 surgical procedures/child with unnoticeable deficit, 1.6/child with moderate involvement and 2.6/child with severe involvement. Also the largest number of survivors were severely involved (66%) compared to unnoticeable (7%) and moderate (27%) involvement.

To develop criteria for the treatment of newborns with myelomeningocele definite prognostic factors must be known. These factors will be determined from evaluation of the causes of the deaths and the quality of life in the survivors compared to the status of the children at birth. With 83% of our children dead or living with severe physical involvement, the development of criteria for treatment has major importance.

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Cover Photograph

"Minnesota 'Medicine' "

In May 1972, after 36 years of practice, mostly and lastly in Moorhead, Minnesota, Dr. H. G. Rice retired. His wife, Jean, and he had long planned on moving to northern Minnesota where they could enjoy a daily "dose" of the medicine provided by it's beautiful lakes and forests.

The cover photo was taken from their home on the east shore of Blue Lake, north of Park Rapids, on a May evening in 1974. He used 35 mm Kodacolor II, ASA 80, a Minolta 7s camera with 45 mm Rokkor lens.

Bacterial Endocarditis 1963 to 1973

Observations on Incidence, Course and Treatment at Minneapolis Veterans Administration Hospital

ROBERT J. KENEVAN* and HORACE H. ZINNEMAN, M.D.†

A review of patients with bacterial endocarditis, as it occurred at Minneapolis Veterans Administration Hospital from 1963 to 1973 established the emergence of staphylococci as the predominant microorganism and an impressive increase in the incidence of *enterococci* as etiologic agents. The review also confirms the relative frequency of neurologic findings. The salient points concerning the individual patient are presented in form of a Table and illustrate that the prognosis of infective endocarditis is favorable in the absence of complications and grave with the appearance of most complications. Prosthetic valve replacement reversed a poor prognosis in seven of 11 patients.

REVIEWS AND BACTERIOLOGIC evaluations of bacterial endocarditis indicate a shift of the involved microorganisms in recent years.[1] Streptococcus viridans seems to have yielded some of its prominence to other microorganisms. This study was undertaken to review not only possible shifts of causative microorganisms but also to evaluate clinical signs and symptoms as well as laboratory findings, which might be helpful in the diagnosis of bacterial endocarditis. A review of the records of Minneapolis Veterans Administration Hospital for the 10-year-period from 1963 to 1973 found 49 patients with the substantiated diagnosis of bacterial endocarditis.

Materials and Methods

After exclusion of all patients with only a presumptive diagnosis, there remained 49 with unquestionable evidence of the disease. The diagnosis in these individuals was based on consistently positive blood cultures, the presence of heart murmurs, petechiae or embolic phenomena, supporting laboratory evidence, such as anemia, leukocytosis, elevated sedimentation rate, the presence of "rheumatoid factor," serum cryoglobulins and in some cases actual inspection of the involved heart valves at surgery or necropsy.

*Phase D student at the University of Minnesota Medical School.

†Departments of Medicine, Minneapolis Veterans Administration Hospital and the University of Minnesota School of Medicine, Minneapolis.

Blood cultures were obtained with aerobic as well as anaerobic techniques in vacuum flasks which permitted aspiration of 10 ml of blood into 100 ml of trypticase soy broth. Cultures were incubated for a maximum of 21 days. Antibiotics were administered according to sensitivity testing by the Kirby-Bauer or tube dilution methods.

The minimal bactericidal serum titer against the offending organism provided an effective guide for the dosage of antibiotic therapy. Bactericidal activity of the serum at a dilution of 1:8 or above was considered desirable. All antibiotics were administered by the intravenous route.

Results

All patients were male, the average age was 56.9 years (Table 1). Twenty-six were known to have had heart disease prior to hospitalization, whereas 23 did not give any indication of prior heart disease or rheumatic fever. Heart murmurs of clinical significance were heard in all but two of the patients, both of whom had staphylococcal endocarditis.

Blood cultures were positive in 45 of the 49 patients (86%). The four individuals with "sterile blood cultures" were included in this study because the diagnosis was documented at surgery in two patients at autopsy in one, and by a convincing array of clinical and laboratory findings in the remaining patient (heart murmur, hypo-

TABLE 1

Pt. No.	Age	Previously known heart disease	Preceding procedure or infection	Involved valves	Blood culture	Antibiotics administered	Surgical intervention	Result
1	70	AS	—	AO	α-strep	Pen.	—	Recovered
2	69	MI	Card. cath.	M	α-strep	Cephalothin	—	Recovered
3	43	AS	—	AO	α-strep	Cephal. + SM	—	Recovered
4	65	—	Pneumonia Brain abscess	AO	S. pneumoniae	Pen. (2 days)	—	Died
5	73	—	Poikiloderma	M	Enterococcus	Amp.-SM	—	Recovered
6	73	ASHD	TUR	M	Klebsiella Enterobacter	Chlor.-Pen.	—	Died Arrhythmia
7	38	AS	Dental surgery	AO	α-strep	Pen.-SM	Starr-Edwards AO Prosthesis	Died. Post-surgical. Arrhythmia
8	35	—	—	AO	Klebsiella Enterobacter	Amp.	—	Recovered
9	58	AS/AI	Dental caries	AO-M	α-strep	Pen.	Prosthesis AO and M	Died
10	34	MI	I.V. drug abuse	M-AO	Enterococcus	Amp.-SM	Prosthesis AO and M	Recovered
11	68	MI	—	M	α-strep	Pen.	—	Recovered
12	67	MI	Dental surgery	M	α-strep	Pen.	—	Recovered
13	60	MI	Dental surgery	M	α-strep	Linco.-SM	Prosthesis-M	Recovered
14	45	MI	Dental exam.	M	Staph-neg.	Naf.-SM	—	Recovered
15	50	—	—	AO-M	Staph-neg.	Diclox.	Prosthesis-AO	Recovered
16	70	—	—	AO	α-strep	Pen.	—	Died (ruptured AO-cusp)
17	73	AS	Proctoscopy Gastroscopy	AO	—	Pen.-SM Linco.-SM	—	Recovered
18	69	MI SBE } prev	Cystitis Cystoscopy	M	Enterococcus	Pen.-SM	—	Recovered
19	36	AS/AI	—	AO	Staph-pos.	Oxacill.	AO-Prosthesis	Died 10 days post-surgery
20	28	—	Dental extr.	M	Staph-neg.	Cephal	—	Recovered
21	65	—	Cystoscopy	AO	Staph-pos.	Oxacill	—	Died. Staph. meningitis
22	35	—	Septal repair Hodgkin's disease GI—hemorrhage	AO	—	Oxacill.-SM	—	Died. Perforated AO cusp. Pericardial effusion.
23	59	AS	Poor dental hygiene	AO	Enterococcus	Pen.-SM	—	Recovered
24	67	—	—	M	Non-hemolytic strep	Pen.	—	Recovered
25	77	—	Pneumonia	M	S. pneumoniae Type II	Pen.	—	Died. CVA, renal failure.
26	77	—	GU tract infection (chronic)	AO	Group A strep	Cephal.	—	Died CHF
27	37	Cong. bicusp. valve	Dental caries	AO	Group A strep	Pen.	AO-Prosthesis	Recovered

Abbreviations:
AI = Aortic insufficiency
AS = Aortic stenosis
MI = Mitral insufficiency
MS = Mitral stenosis
RF = Rheumatic fever
AO = Aortic valve
M = Mitral valve
Tric = Tricuspid valve
α-strep = α-hemolytic streptococcus
Staph-pos. = DNAse positive staphylococcus
Staph-neg. = DNAse negative staphylococcus
Pen. = Penicillin-G
SM. = Streptomycin
Amp. = Ampicillin
Chlor. = Chloramphenicol
Linco. = Lincomycin
Naf. = Nafcillin
Diclox. = Dicloxacillin
Oxacill. = Oxacillin
Cephal. = Cephalothin
Genta. = Gentamicin

TABLE 1 (Continued)

Pt. No.	Age	Previously known heart disease	Preceding procedure or infection	Involved valves	Blood culture	Antibiotics administered	Surgical intervention	Result
28	49	RF	Carotid endarterectomy	M	α-strep	Pen.	—	Improved. (died 13 mos. later, surgery)
29	24		I.V. drug abuse	Tric	Staph-pos.	Oxacill.	—	Recovered
30	46	MI/MS	—	M	Staph-neg.	Pen.	—	Recovered
31	74	—	—	M	Staph DNAse + (at autopsy)	—	—	Admitted with CVA. Died.
32	73	—	TUR GU infect	M	Enterococcus	Amp.-genta.	—	Recovered
33	26	Cong. bicusp. AO valve	—	AO	Enterobacter at autopsy	Pen.-SM	—	Died. Subarachnoid hemorrhage
34	78	—	—	AO	α-strep	Pen. Linco.	—	Improved. Died later of CHF
35	58	AS	Dental abscess	AO	Staph-pos.	Oxacill.	—	Recovered
36	77	—	TUR	M	Enterococcus	Amp.	—	Recovered
37	61	—	Surgery for abdominal abscess	AO	Staph DNAse +	Cephal.	—	Recovered
38	53	RF	—	AO-M	α-strep	Pen.-SM	—	Improved (died 3 mos. later of CHF)
39	51	—	Cellulitis	M	Staph-neg.	Naf. Linco.	—	Recovered
40	77	Calcif A.S.	TUR GU infection	AO-M	Enterococcus	Amp.	—	Died
41	56	—	Pneumonia	AO	γ-strep	Pen.-SM	—	Recovered
42	25	—	I.V. drug abuse	AO	Staph-pos.	Oxacill.	—	Recovered
43	58	—	Osteomyelitis	AO	Staph-pos.	Oxacill.	—	Recovered
44	50	—	Pneumonia	AO	S. pneumoniae	Pen.	AO-Prosthesis	Recovered
45	59	—	Psoriasis with derm. infection	M	—	Pen.-SM	—	Recovered
46	77	RF 55 yrs prev. SBE 13 yrs prev.	—	M	Staph-neg.	Pen.	—	Died. Aspir. pneumonia
47	43	RF	—	AO-M	—	Pen.-SM	—	Recovered
48	52	MI	—	M	α-strep	Pen.	—	Recovered
49	76	—	—	M	Staph-pos.	Naf.	—	Died. (Staph. meningitis

chromic anemia, leukocytosis, elevated sedimentation rate, petechiae, hematuria, proteinuria, positive latex fixation for rheumatoid factor).

Table 2 shows the change in bacteriologic findings which has taken place in the past two decades. Alpha hemolytic streptococci are no longer the predominant pathogen. Staphylococci have taken their place. Eight of the 15 patients with staphylococcal endocarditis had no history of prior heart disease or rheumatic fever.

TABLE 2

Incidence of microorganisms cultured from the blood of patients with bacterial endocarditis.

Staphylococci	15
DNAse positive: 9	
DNAse negative: 6	
Streptococcus mitis (viridans)	13
Enterococcus	7
Streptococcus pneumoniae	3
Klebsiella-enterobacter	3
Group A streptococci	2
No organism cultured	4

Presumptive foci of infection were identified in 32 of the 49 patients (Table 3).

Forty-four had been febrile for an average of 56 days prior to hospitalization. At the time of admission body temperatures ranged from 99.2 to 105°F (mean 101.2°). Five patients were afebrile at the time of hospitalization. Blood cultures yielded DNAse negative staphylococci in four of them and a non-hemolytic streptococcus in the fifth.

TABLE 3

Preceding infections or procedures which may have been sources of bacteremia.

Skin infection	3
Pulmonary disease	3
Intravenous drug abuse	3
Urologic infection and/or procedures	8
Dental surgery or infection	8
Endarterectomy	1
Osteomyelitis	1
Minor surgery	2
Immunosuppressive and cytotoxic therapy	1

Body temperatures of 50% of the patients returned to normal within three days after initiation of antibiotic therapy. The average period for all 49 patients however was 6.7 days.

Cutaneous phenomena of clinical significance were observed in 23 patients (petechiae in 12, splinter hemorrhages in 10 and Osler nodes in 1). Roth spots were seen in the retinae of two individuals, and one suffered multiple gangrenous areas of digits, presumably due to emboli.

Central nervous system involvement was observed in 18 patients (Table 4). Hemiplegia was the presenting symptom in two of them. Microscopic hematuria was found in 27 patients, nine of whom also had granular red cell casts, proteinuria and pathologically elevated blood urea nitrogen, suggesting glomerulitis.

TABLE 4

Incidence of central nervous system involvement in 18 of 49 patients with bacterial endocarditis.

Coma	5
Cerebrovascular accident*	5
Confusion	4
Meningitis	2
Subarachnoid hemorrhage	2

*Presenting symptom in two patients.

Ten patients had enlarged spleens. Blood hemoglobin concentrations at the time of hospital admission ranged from 6.1 to 17.6 gm/100 ml (mean 11.5 gm/100 ml). Neither duration of the disease, nor the type of infecting microorganism seemed associated with the presence or extent of anemia. Successful antibiotic therapy resulted in prompt but gradual increase of hemoglobin concentration.

The mean white blood cell count was 10.822/cu mm (4,300-454,000). The extent of leukocytosis was not characteristic of any particular type of microorganism, although the highest WBC (45,400) was found in endocarditis due to *S. pneumoniae*.

Sixty percent of the blood sera agglutinated γ-globulin-coated latex particles at some period of the disease.

Endocarditis due to penicillinase-producing staphylococci was treated with oxacillin or nafcillin, and in cases of penicillin allergy with cephalothin, in intravenously administered doses from 10 to 12 gm per day for a duration of 26 to 42 days. Minimal bactericidal serum titers of 1:8 were maintained during the treatment period.

Alpha-hemolytic streptococci were treated with either 20 million units of penicillin G for 28 days or in combination with streptomycin 1 gm daily for the first two weeks and penicillin G alone for an additional two weeks.[2-4] In two patients with penicillin allergy i.v. administration of six gm of lincomycin per day proved successful.

Enterococci were cultured from the blood of seven patients. Antibiotic sensitivity patterns in two of these patients suggest in retrospect, that their disease might have been due to *Streptococcus bovis*.[5-7] Five were treated for 30 to 54 days with combinations of penicillin and streptomycin or ampicillin and gentamicin, whereas ampicillin alone was satisfactory for two.

Valvular infections with pneumococci or group A streptococci were treated either with penicillin alone or with a combination of penicillin and streptomycin.

Thirty-six patients recovered, whereas 13 succumbed to complications, such as congestive heart failure (7), cerebrovascular accidents (2), meningitis (3) and subarachnoid hemorrhage (1).

Not all 17 patients who developed congestive heart failure during the disease had a poor prognosis. Six recovered adequate myocardial competence under conservative treatment. Prosthetic valve replacement became necessary in 11 (seven aortic, two mitral, two double valve replacements) and was successful in seven of the 11 patients.

Discussion

The statistical data of this study are essentially in agreement with other studies of similar nature. Differences reflect our particular type of patients. Involvement of the aortic valve in 24 patients reflects the preponderantly male population of this hospital. Sex as well as age group are the reason for the high incidence (16%) of preceding infections or procedures involving the urinary tract.

Involvement of the central nervous system in 36% of our patients meets the generally reported incidence and lies between Jones' report of 29%[8] and Ziment's of 50%.[9] Variations between individual reports probably reflect the interpretation and documentation of minor neurological signs.

Multiple blood cultures resulted in the isolation of responsible pathogens in all but four of our patients. One of the latter had been transferred

to this institution after several days' administration of antibiotics. Failure to isolate the etiologic microorganism in the remaining three may have been due to high bactericidal factors within the serum, or perhaps to anaerobic techniques, which were not as sophisticated at the time than the ones employed at our institution today. The entity of endocarditis caused by anaerobic microorganisms has been well established.[10,11]

Chronic hemodialysis was not an etiologic factor in any of our patients in spite of an active program of renal hemodialysis and transplantation at this hospital. It has been a problem elsewhere[12-14] and may be seen here in the future.

Two episodes of bacterial endocarditis due to *Pseudomonas maltophilia* were not included in this group, since their infection occurred during extracorporeal perfusion at the occasion of surgical insertion of prosthetic (Starr-Edwards) valves. Both happened within one week and are undoubtedly due to contamination of the perfusion arrangement, although this could not be traced to a definite source. It has not occurred previously or since.

Minimal bactericidal concentration of antibiotics in a patient's serum (MBC) has been a useful guide to antibiotic therapy. Bacteriologic cure is possible however, in the absence of an effective MBC, if the minimal inhibitory concentration (MIC) is adequate. This could be observed in patient No. 34 who was treated with lincomycin because of allergy to penicillin. The effect was curative, as far as his valvular infection was concerned. Several weeks after completion of therapy he succumbed to congestive heart failure, and inspection of his aortic valve at necropsy showed complete healing. In general, however, one should be satisfied with no less than a bactericidal serum concentration of antibiotics at a titer of 1:8.

Although we observed multiple episodes of candidemia none of those patients developed endocarditis due to *Candida albicans*.

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Children's Hospital—St. Paul

Dr. Stephen Boros of Minneapolis was named Director of Neonatology at the Children's Hospital, St. Paul.

Beginning last July he will direct the Hospital's 30-bed Regional Newborn Intensive Care Center and will supervise the care of over 400 infants each year transferred from hospitals throughout Minnesota and western Wisconsin.

In addition, he is an Assistant Professor in Pediatrics at the University of Minnesota.

Alcoholic Hepatitis with Leukemoid Reaction and Thrombocytosis

HANS R. BAUR, M.D.;* CLAUS A. PIERACH, M.D.;* G. JEELANI DHAR, M.D.* and GÜNER GÜLMEN, M.D.*

We report a fatal case of alcoholic hepatitis in a 37-year-old man who presented with a leukocyte count of 82,000/mm³ and a platelet count of 700,000/mm³. No concomitant disease was found at autopsy. The pathogenesis of this unusual hematological complication is obscure, but possible explanations are: (1) A toxic or allergic irritation of the bone marrow and (2) Infection with a "leukovirus."

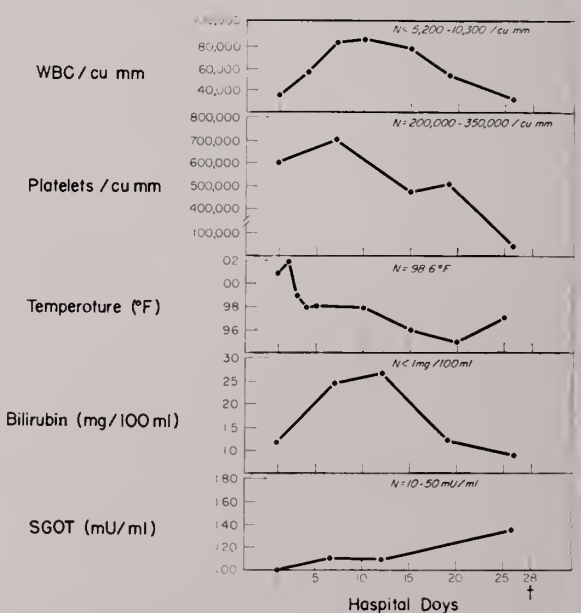
A MODERATE LEUKOCYTOSIS and thrombocytopenia are often seen in patients with alcoholic hepatitis. A marked increase in these two blood elements is rarely seen in liver disease, and the simultaneous occurrence of a leukemoid blood picture together with a thrombocytosis in alcoholic hepatitis has, to our knowledge, not yet been described.

Case Report

A 37-year-old white man was admitted to Northwestern Hospital on September 27, 1972, with anorexia, nausea, and vomiting, starting in January, 1972. In September of 1972, his abdomen became tender and distended, he developed jaundice, and suffered from a chronic diarrhea with gray and discolored stools. The patient had consumed large quantities of beer and whiskey for 20 years and drank a pint of whiskey a day for the four years prior to admission.

On admission, he was well developed and in no acute distress, but deeply jaundiced. His temperature was 101°F, pulse 100, and the blood pressure 100/80 mm Hg. The abdomen was distended and tender. Shifting dullness and a positive fluid wave were present. A tender, sharp liver edge was palpated 15 cm below the right costal margin. The testicles were atrophic. The skin showed bilateral palmar erythema and a few spider nevi. There were no abdominal varicosities. The ankles were edematous.

Laboratory data revealed the following values: Hemoglobin 11.7 gm/100 ml; hematocrit 37%; red blood cells 2.6 million/mm³; mean corpuscular volume 128 μ^3; leukocytes 34,900/mm³ with 90% neutrophils, 6% lymphocytes, 1% monocytes, and 3% eosinophils; reticulocytes 13.0%; platelets 606,000/mm³; total serum protein 5.7 gm/100 ml; serum albumin 1.41 gm/100 ml; total bilirubin 11.8 mg/100 ml, rising in a few days to 24.5 mg/100 ml; cholesterol 555 mg/100 ml; triglycerides 388 mg/100 ml; lipid electrophoresis: Type II hyperlipidemia; serum glutamic oxaloacetic transaminase 111 U; alkaline phosphatase 545 U; lactate dehydrogenase 103 U; prothrombin time 14.7 sec with a control of 11.5 sec; bone marrow: 0.8% myeloblasts, 2.4% promyelocytes, 72.8% myelocytes, 8.8% metamyelocytes, 3.6% mature neutrophils, 1.8% lymphocytes, 9.2% normoblasts, 0.6% plasma cells, no eosinophils or basophils, normal number of megakaryocytes, orderly cell maturation, increased



Figure—Clinical and Laboratory Course.

*University of Minnesota Unit of Teaching and Research in Internal Medicine at Northwestern Hospital, Minneapolis, Minnesota.

Requests for reprints should be addressed to Dr. Claus A. Pierach, Northwestern Hospital, 810 E. 27th Street, Minneapolis, MN 55407.

stainable iron present. Details of his clinical course are depicted in the Figure.

Upper gastrointestinal roentgenograms showed esophageal varices. Blood culture was negative. His *hospital course* was characterized by three major problems:

Portal Hypertension

After an initial loss of 3 kg, his ascites did not decrease appreciably, despite water and salt restriction, diuretics, and two paracenteses. In the third week of hospitalization, he had a massive gastrointestinal hemorrhage necessitating transfusion of 1,000 ml of blood.

Hematological Complications

After one week, the leukocyte count rose to 82,500/mm^3, with a differential count of 70% segmented neutrophils, 16% bandform neutrophils, 5% lymphocytes, 2% monocytes, 3% metamyelocytes, and 4% myelocytes. The platelet count rose to 700,000/mm^3. Leukocyte alkaline phosphatase was elevated to 212 per 100 mature polymorphonuclear leukocytes with a control of 171. Because of this striking leukemoid reaction and thrombocytosis, and the rapid and massive development of the ascites refractory to any treatment, the possibility of polycythemia producing a Budd-Chiari syndrome was entertained. However, the liver biopsy showed only pathological changes of acute alcoholic hepatitis, and bone marrow examination revealed a nonspecific myeloid hyperplasia.

Renal and Electrolyte Complications

The patient's serum sodium level dropped continuously to values around 110 meq/liter. His urine output decreased. His blood pressure dropped, and he died in hepatic and renal failure on the 28th day of his hospitalization.

At autopsy, the liver weighed 3,000 gm; it had a tense capsule and a greasy cut surface. Microscopic examination revealed a widespread liver cell necrosis, fibrosis, alcoholic hyaline, and infiltration with polymorphonuclear leukocytes, especially in the central lobular areas. There was also some cholestasis. The spleen weighed 250 gm; it showed engorged sinusoids and small periarterial lymphoid sheaths. The autopsy also revealed: ascites (four liters), esophageal varices, focal pancreatitis, testicular atrophy, and granulocytic hyperplasia in the bone marrow.

Discussion

This patient presented the typical natural history of severe alcoholic hepatitis.[1-4] The moderate elevation of SGOT, high alkaline phosphatase and cholesterol are often found in this condition.[2-5] Bilirubin levels were high, which is considered a sign of extensive liver damage with poor prognosis.[6] His serum sodium dropped rapidly below 125 meq/liter an ominous sign often indicating impending renal failure.[7]

Because of unusual hematological abnormalities, we considered a concomitant disease. His high leukocyte alkaline phosphatase did not indicate chronic myelocytic leukemia, the bone marrow showed orderly cell maturation, absence of basophils, and a normal number of megakaryocytes, and autopsy gave no evidence of a myeloproliferative disorder. The morphology of his white cells was normal. At autopsy, polymorphonuclear infiltration was seen in areas of pancreatic fat necrosis, as well as in the liver. His jaundice, anemia, and hyperlipidemia were suggestive of Zieve's syndrome,[8] which occurs in alcoholic hepatitis.[4] Leukemoid reactions[9] are found in infections, toxic states, and neoplasms. In alcoholic hepatitis, they are rare.[2] They have been reported in patients with severe hepatic damage due to viral hepatitis, drug hypersensitivity, and disseminated tuberculosis. Though the white blood cell count is typically elevated in alcoholic hepatitis, it seldom exceeds 30,000/mm.[3] The cause of the blood picture in general is still an enigma, but an extreme toxic or allergic irritation of the bone marrow has been discussed,[10] in cases of alcoholic hepatitis, perhaps due to products of the massive liver cell necrosis released into the blood. Moore and associates[11] proposed that the leukemoid reaction is caused by a specific "leukovirus" which can grow only in severely debilitated patients. In fact, they were able to demonstrate such a "leukovirus" in hematopoietic cells of a patient with a malignant melanoma presenting with a leukemoid blood picture.

Chronic alcoholics often present with a platelet count below 150,000/mm^3.[12] The mechanism of this depression is not known, but it is likely that alcohol per se causes a reduction of the circulating platelet number and a shortened platelet survival.[12,13] The morphology and function of the platelets in our case were unremarkable; no abnormal bleeding or clotting tendency was noted. Thrombocytosis in chronic alcoholics is rare, and only recently was it recognized that a small number of alcoholics with cirrhosis[14] or alcoholic hepatitis have increased platelet counts, the cause of which is not known. A rebound thrombocytosis following thrombocytopenia after alcohol withdrawal has been demonstrated in a few patients.[12] Our patient might have been in this rebound phase, as he had stopped drinking eight days prior to admission. A response to the correction of a folic acid deficiency with the normal hospital diet is another explanation for this phenomenon.[14] Many different clinical disorders often associated with tissue inflammation and necrosis can produce secondary thrombocytosis with or

without leukocytosis.[14] It may be that damaged tissue releases factors which are able to stimulate these two cell lines.

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MSMA Annual Meeting

As Time Goes Bi-. . .

The entire country is playing As time goes Bi-. Bicentenniel, that is. And in planning the 1976 Annual Meeting, the MSMA is jumping on that tradition laden band wagon that started rolling some 200 years ago. The theme, "Chirurgical and Medical Emergencies, '76," once again emphasizes continuing medical education. The likes of Thomas Jefferson might identify with the spelling of surgical. But, that's where the similarities of yesterday and today end. In fact, our 1976 meeting agenda is so timely, I've taken a cue from popular advertising slogans to best explain what's being planned for you.

We heard you. Yes, you came across loud and strong at the St. Paul Meeting. We heard the accolades regarding program content, speakers, format. We also heard complaints concerning crowded facilities, time conflicts, and pre-registration. And, we're trying to eliminate such negatives in Rochester.

We know what physicians are looking for. We know from the evaluation cards submitted by 50% of St. Paul attendees that you want more limited registration sessions, seminars allowing more discussion and the intimacy for better question and answer periods. We know you want scientific programs that teach you something you don't already know, programs that are challenging and constructive, purposeful and can be put to practical use in the office.

MSMA does it all for you. That's right. The entire scientific program is planned for you, the Minnesota physician, and your continuing education. Not only do CME credits stack up to keep you an MSMA member in good standing, but they keep you current on those topics that can't be adequately covered in print media. The social events let you enjoy your favorite pastimes while you enjoy the company of members from the entire state. The activities of the House of Delegates meet today's issues with policy forming, legislative influencing, public enlightening answers which reflect your needs and affect your daily practice.

We heard you. We know what physicians are looking for. MSMA does it all for you. You can count on us to make this year's Annual Meeting a pleasure for you. And, we hope that you'll let it be our pleasure to welcome you to Rochester, May 19-21, 1976!

Watch for more news on CME '76 in subsequent issues!

R. D. Semsch, M.D.
Chairman
Scientific Assembly

Transthoracic Electric Impedance

A Clinical Guide of Pulmonary Fluid Accumulation in Congestive Heart Failure

MARCOS U. RAMOS, M.D.;* JOHN W. LaBREE, M.D.;† WILLIAM REMOLE, M.D.†
and WILLIAM G. KUBICEK, Ph.D.*

This nonivasive technique has been found to be a reliable method to monitor the fluid shifts in patients with congestive heart failure. These data show that despite the marked initial diuresis and weight loss, the pulmonary congestion is not relieved until adequate digitalization is accomplished. The poor correlation between the usual clinical criteria of improvement and the actual severity of the pulmonary congestive process is discussed.

THE USE OF ELECTRICAL impedance in the detection of physiological events is a simple technique requiring only the passage of an electrical signal through biological tissues, thus including them as part of an electrical circuit in the form of a volume conductor. The drop in voltage due to the impedance of all the biological tissues encompassed in that volume conductor can be detected by means of pick-up electrodes. This technique offers the advantage that no specialized transducers are required since the electrodes themselves detect the changes which occur to the signal originally fed into the system. The method also offers the advantage of being noninvasive.

Most clinicians are aware of the difficulty in evaluating quantitatively the severity and the extent of pulmonary congestion and edema resulting from heart failure. In recent years many authors[1-8] have reported changes in transthoracic electrical impedance caused by shift in the fluid content of the thorax. The changes in transthoracic electrical impedance have been found to correlate linearly with the intrathoracic fluid volume changes.

*Department of Physical Medicine and Rehabilitation, University of Minnesota Medical School, Minneapolis, Minnesota.
†Department of Medical Education, St. Mary's Hospital, Minneapolis, Minnesota.
Reprint requests to: Marcos U. Ramos, M.D., U.S. Army Research Institute of Environmental Medicine, Natick, Massachusetts 01760.
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The electrical impedance of the thorax is the resultant of the impedance of all the tissues; the volume and quality of the biological fluids and gases contained within it. Hence, two different bioelectrical factors are readily identifiable as responsible for this phenomenon; one constant and one variable. The electrical characteristics and distribution of bone, muscle, fat, connective tissue, heart, and lungs remain relatively stable resulting in a constant factor. The movement of gases and fluids due to cardiopulmonary function constitutes the variable factor. The low impedance of body fluids compared to the high impedance of air makes the former the most significant component of the variable factor and hence the most important fraction responsible for the change in transthoracic electrical impedance during these observations.

Several investigators[4,5,10] have observed a linear relationship between the change in transthoracic electrical impedance and the change in intra and extravascular fluid induced in experiments on animals. Others[1] using rigidly controlled experimental animal models, have been able to quantify the amount of pulmonary fluid volume change using the change in thoracic electrical impedance. Luepker, et al.[4] have reported on the changes in thoracic impedance during the development of acute pulmonary edema, in dogs, produced by elevating the left mean atrial pressure.

The need for development of repeatable, noninvasive means to monitor patients in congestive

heart is obvious to the clinician dealing with these patients. The purpose of this investigation was to study the changes in transthoracic electrical impedance (TEI) during the clinical treatment of three patients with the diagnosis of acute congestive heart failure.

Methods and Procedures

Daily transthoracic electrical impedance measurements were taken in three patients in whom the diagnosis of acute congestive heart failure was established. Impedance measurements were taken on admission and daily at the same time during the day during the acute period. In one of the patients, more frequent readings were obtained. The transthoracic electrical impedance was recorded using the Minnesota Impedance Cardiograph, Model 304, described by Kubicek and associates.[11-13] The technique requires the placement of four circular aluminized mylar electrodes at: (1) the level of the upper neck, (2) thoracic inlet at the base of the neck, (3) the level of the xiphisternal junction, and (4) the upper abdomen (Figure 1). Electrodes (1) and (4) are activated by a constant current source at a frequency of 100 KHz with a current of 4 mA. The drop in voltage is picked up by the two inner electrodes (2) (3) and fed into a high-input impedance amplifier. The transthoracic electrical impedance (Z_o) is displayed on a digital panel meter (Figure 1). The distance (cm) between the two pick-up electrodes is measured anteriorly and posteriorly and averaged (L). The changes in transthoracic electrical impedance are reported as the ratio Z_o/L in ohms per centimeter.

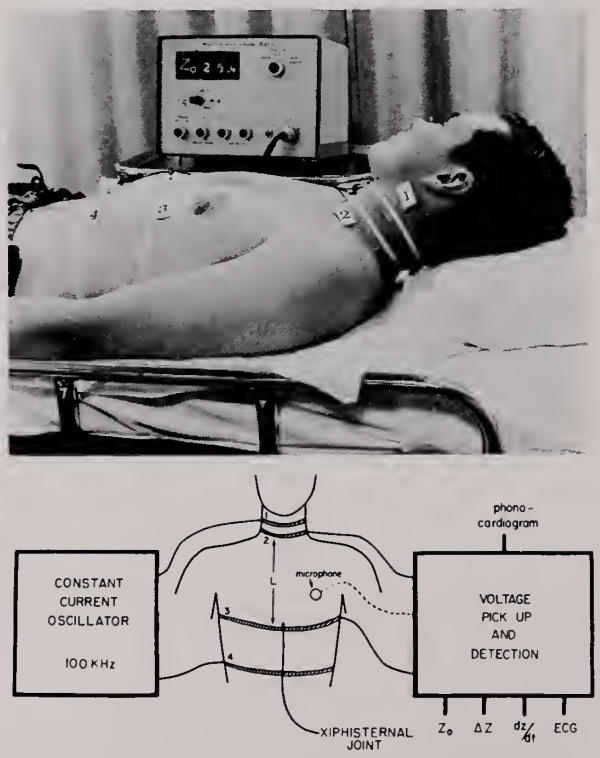


Fig. 1—Photograph of the subject with the tape electrodes in place. The digital readout demonstrates the transthoracic impedance recorded between electrodes 2 and 3. The diagram shows the electrode configuration and the basic electrical circuit.

The recordings were taken at specific times during the day to avoid variables introduced by hospital routines and meals. Extreme care was taken when placing the two pick-up electrodes and, when possible, the electrodes were left in place for several days. If the electrodes were removed the skin was marked and on subsequent recordings the electrodes were repositioned according to the markings with an error in repositioning of $\pm$ 0.5 cm.

Following placement of the electrodes the patient was allowed to rest supine with a pillow for 15 minutes. The recording was taken after 10 additional minutes of resting supine without a pillow. The impedance recorded was the one shown at the end of a normal expiration. Three sequential readings were taken and averaged. The patient's weight, fluid intake and output, the most current Xray, and the physicians' and nurses' clinical impressions were recorded whenever available.

Controls

Several authors[4] have mentioned the difficulty in standardizing the electrode placement when taking multiple recordings. In an attempt to minimize this difficulty the transthoracic electrical impedance was recorded as the ratio Z_o/L (ohms per centimeter). The ratio Z_o/L measured in sixty normal subjects (30 men and 30 women) in supine position showed a range of 0.822 $\pm$ 0.021 SEM for men and 1.094 $\pm$ 0.0184 SEM for women.

In order to evaluate the effect of variations in the distance between the pick-up electrodes the transthoracic electrical impedance ratio Z_o/L was measured in three normal subjects according to protocol. Several sets of recordings were also taken while purposely varying the distance (L) between the pick-up electrodes (2 and 3). The Z_o/L values were plotted against the value of L in order to determine the effects of changes in L on the ratio Z_o/L.

Results

On admission the ratio Z_o/L for all three patients was found to be below normal values indicating an excessive accumulation of conductive fluid in the thoracic cavity. This phenomenon was supported both clinically and radiographically. The patients were treated in the usual manner with semi-recumbent bed rest, diuretics (Furosemide and Ethacrynic Acid), and two of them received digitalis. The third case, was found to be in digitalis toxicity; thus, digitalis was discontinued.

The clinical courses of two cases who eventually recovered, were quite similar. A 22-year-old man was four months post-aortic and a mitral valve replacement. He was admitted in congestive heart failure secondary to mitral regurgitation. At the time of admission he was partially digitalized. He was treated with diuretics and digitalis. Several hours after the institution of therapy, rapid diuresis was observed along with corresponding weight loss. The total diuresis in the initial 24 hours was reflected by an eight kg weight loss (Figure 2). After this weight loss, his weight became stable for the next two days. The total weight loss in the four days following the initial 8 kg weight loss was 2.5 kg for a total of 10.5 kg.

It is clear that as a result of the diuretic therapy there was a rapid weight loss in the initial 24 hours followed by a slower rate in subsequent days.

The transthoracic impedance ratio (Z_o/L) on admission was very low indicating an excessive accumulation of electrolytic fluid in the thoracic cavity. This value showed minimal change in the first 24 hours at the time when the weight loss was most rapid. No significant change was noticed in the second day either. During the third day after admission a sudden steep rise in the impedance ratio was observed indicating a marked exit of the thoracic fluid accumulation. Thereafter, the impedance ratio continued increasing approaching a normal value after five days of therapy. It is clear that mobilization of the thoracic fluid accumulation occurred only after the third day of therapy even though the total water loss (diuresis) occurred mostly in the first day of therapy.

The second case showed a similar trend. He was a 51-year old hypertensive man admitted in acute congestive heart failure. There was no previous history of cardiac decompensation. He was treated with diuretics (Furosemide) and digitalis. The first three days of therapy resulted in a 9.5 kg weight loss due to diuresis (Figure 3). There-



Fig. 2—This figure shows the daily recordings of the transthoracic impedance ratio (Z_o/L) and the body weight change. The brackets on each point of Z_o/L represent the margin of error due to repositioning of the electrodes (Figure 5). Note that the most rapid weight loss occurred within the first 24 hours; thereafter, the weight loss was minimal. The Z_o/L curve shows that the most rapid exit of the thoracic fluid accumulation occurred only after the second day. The x-ray photographs demonstrate minimal changes between the one taken on admission and the one taken on discharge.

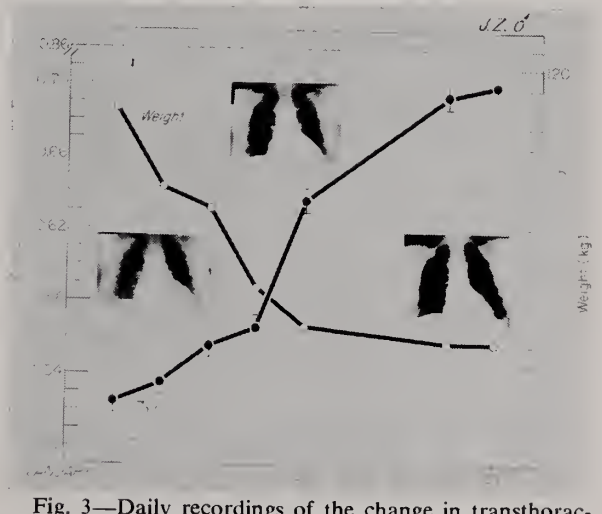


Fig. 3—Daily recordings of the change in transthoracic electrical impedance (Z_o/L) and the daily weight change. The symbols used and the scales are similar to the ones on Figure 2. The most rapid weight change occurred during the first three days of therapy. The Z_o/L curve shows its sharpest rise after the third day indicating that the exit of the thoracic fluid accumulation occurred at this point rather than coincidental with the initial marked diuresis. The Xrays shown demonstrate reduction in the heart size and clearing of the pulmonary vascular markings. The dotted line at 0.86 represents the ratio Z_o/L recorded in 30 normal males in supine position.

after, the weight loss was small; 2.5 kg in three days.

The transthoracic impedance ratio showed a small rise in the first three days (from 0.52 to 0.56). In the fourth day of therapy a steep rise on the thoracic impedance ratio marked the rapid removal of the thoracic fluid volume. The mobilization of fluid continued through the fifth day tapering off on the sixth day upon approaching the normal value. It is obvious that there was a lack of correlation between the total body fluid loss due to diuresis and the actual mobilization of the excessive fluid accumulation in the thoracic cavity in congestive heart failure. The third case had an unfortunate clinical course. More frequent transthoracic electrical impedance recordings were taken than in the other cases. Whenever possible, these have been correlated with clinical observations. She was a 78-year old female with a long history of congestive heart failure. She was admitted with the diagnosis of severe congestive heart failure and digitalis toxicity. She was treated with diuretics (Ethacrynic Acid), oxygen and semi-recumbent bed rest. Digitalis was discontinued.

Four hours after admission and after the initial Z_o/L recording she went into a cardiac arrest which was successfully treated. She was placed on ventilatory assistance by means of an intermittent positive pressure respirator. The effect of this procedure, i.e., increase in the functional residual capacity was not assessed. Z_o/L recordings in the hours following this episode were extremely low. Plotting of these values showed an over-all downward slope in the first twenty-four hours after arrest (Figure 4). During the initial 24 hours after arrest she was described as "responding." Toward the end of this period she was described as "clear, blood gases satisfactory," and later as "talking with her family, stable." Her urinary output in the first 24 hours was 1775 cc's. Forty-eight hours after the cardiac arrest the ratio Z_o/L reached a higher value but still far below normal. At that time she was taken off the respirator and described as "alert and cooperative." Thereafter, the ratio Z_o/L continued to show a downward trend despite her improved clinical picture and diuresis.

Five days after the cardiac arrest she was described as confused, later unconscious, and she finally expired.

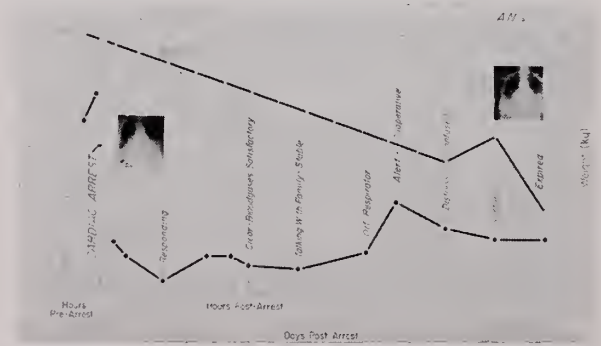


Fig. 4—This figure shows the changes in transthoracic electrical impedance (Z_o/L) and weight change. The weight curve is indicated with a broken line during the first three days since no weight was recorded in these days. Notice the poor correlation between the clinical impression and actual amount of pulmonary congestion and thoracic fluid volume as evidenced by the ratio Z_o/L. The dotted line at the level of 1.09 represents the ratio Z_o/L recorded in 30 normal women in supine position. All other symbols and scales used are similar to the ones described in Figure 2.

Controls

The transthoracic impedance ratio Z_o/L obtained in the three controls fell within the range of normal found on thirty normal men in the supine position (0.86 ± 0.021 SEM). There was a negligible variation in the ratio Z_o/L even when the electrodes were grossly displayed (see Figure 5). As it can be seen from this figure, a ± 0.5 cm error in reposition of the electrodes in patients with previous skin marks results in a 0.015 ohms/cm variation.

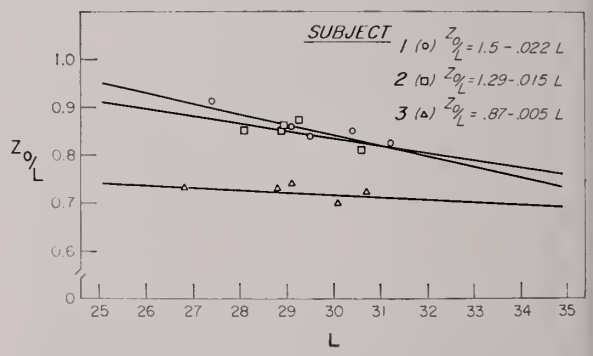


Fig. 5—This figure shows the changes in the ratio Z_oL as a function of L (in cm). Assuming an error in repositioning of the tapes on a patient with previous skin marks of ± 0.5 cm, the resultant error in the ratio Z_o/L is 0.015 as calculated from subject 2. This margin of error in repositioning is indicated by the brackets on the Z_o/L curves on Figures 2, 3 and 4.

Discussion

Although of recent development, the use of transthoracic electrical impedance as an indicator of conductive fluid shifts in the thorax have been well documented.[1,2,4-7,11-13] The exact quantifica-

tion of the fluid shifts using the non-invasive method require a rigid control of the experimental conditions possible only in experimental animals. Nevertheless, the accuracy of the method to indicate depletion of accumulation of conductive fluid in the thoracic cavity is highly reliable[1,2,4,5,9,10] making this method an excellent one in the clinical monitoring of patients in congestive heart failure. This method is non-invasive, easily applied and the data are readily available on the digital panel meter making its use easy for paramedical personnel.

Analysis of the body weight change versus the impedance change shows a peculiar relation in two of the patients. In spite of the marked weight loss and diuresis during the initial treatment period, the thoracic impedance showed minimal simultaneous change. The most rapid impedance change occurred 48 hours after the initial weight loss in one case and 72 hours in the other. The first case was partially digitalized and the second one was started on digitalis at the time of admission.

On the basis of this observation several conclusions can be reached and possible explanations offered. It is evident that in the recovery from congestive heart failure, which produced both peripheral and pulmonary edema, there was an initial elimination of peripheral fluid volume before any significant reduction of pulmonary fluid volume occurred.

It is well known that pulmonary congestion and transudation of fluid out of the pulmonary capillaries occur as a result of an increase in the pulmonary capillary pressure produced by an elevated left atrial pressure. Coincidental with these pulmonary events, the failing left ventricle shows an elevated end diastolic pressure, increase in diastolic and systolic volumes, diminished ejection fraction and produces an increased left atrial pressure. From these findings it is clear that pulmonary congestion or edema resulting from a failing left ventricle will only be cleared if the pumping ability of the left ventricle is improved.

The occurrence of generalized venoconstriction along with the redistribution of blood into the more distensible, central pulmonary vascular bed has been described by many authors.[14-16] That this phenomenon is a significant one in the production of the symptoms observed in congestive heart failure is evidenced by the remarkable improvement both hemodynamically (collapse of the neck veins) and systemically after 10 minutes of intravenous administration of hexamethonium.[17] Hexamethonium, a sympathetic ganglionic blocking agent, greatly reduces the venous pressure.

The potent diuretics currently in use will cause a sharp reduction in the amount of fluid handled by the failing ventricle, thus causing a decrease in the work of the heart. Their action generally starts within 30 minutes after a single dose and it is largely completed in six hours.[18] Despite this fluid depletion, it is clear that the pulmonary vascular congestion and edema resulting from the pulmonary venous obstruction due to the increased left atrial pressure will continue until left ventricular function improves.

It is reasonable to assume that the rapid rise in the transthoracic electrical impedance noticed in two of the patients, 48 to 72 hours after the initiation of therapy, occurred as a result of digitalis improving left ventricular function.

The results on these two patients who improved appear to be in agreement with the ones reported by Rader et al.[14] in their Group 2. This group of patients in congestive heart failure obtained a good diuresis and "some subjective improvement" when treated only with diuretic therapy. No improvement in cardiac output or arterial-venous oxygen difference was noticed. These physiological parameters returned to normal only after full digitalization. Although the relationship between the weight loss and the change in thoracic impedance is being reported in only two patients, this serves to point out the difficulties in the objective assessment of the treatment of clinical congestive heart failure.

The effects of the increase in functional residual capacity induced by ventilatory assistance on the transthoracic electrical impedance have been addressed in several reports.[5-10] Since the third case was placed on ventilatory assistance this possible effect should be considered in the interpretation of the data. It is reasonable to speculate that if this increase was of sufficient magnitude it may have altered the ratio Z_o/L. If this was the case, this would have been reflected in a rise in the Z_o/L, since this value only reflects the amount of electrolytic fluid in the thoracic cavity. The fact that inspite of this potential effect, the ratio Z_o/L stayed far below normal values seems to indicate that the extent of the pulmonary conges-

tion was indeed severe.

The last case serves to point out the poor correlation between the clinical observation and the actual severity of the pulmonary congestion. Others[14] have expressed this frustration observing that "neither the classical symptoms of the patient nor the objective evidences of elevated venous and intracardiac pressures, both produced by the circulatory congestion and long the traditional bedside indices of heart failure can serve to indicate the status of the cardiac function."

The changes in the electrical impedance of the thoracic cavity, reflect accurately the change in its fluid content. The ease of its application and interpretation makes it a very promising tool for the objective evaluation of the pulmonary congestion in heart failure.

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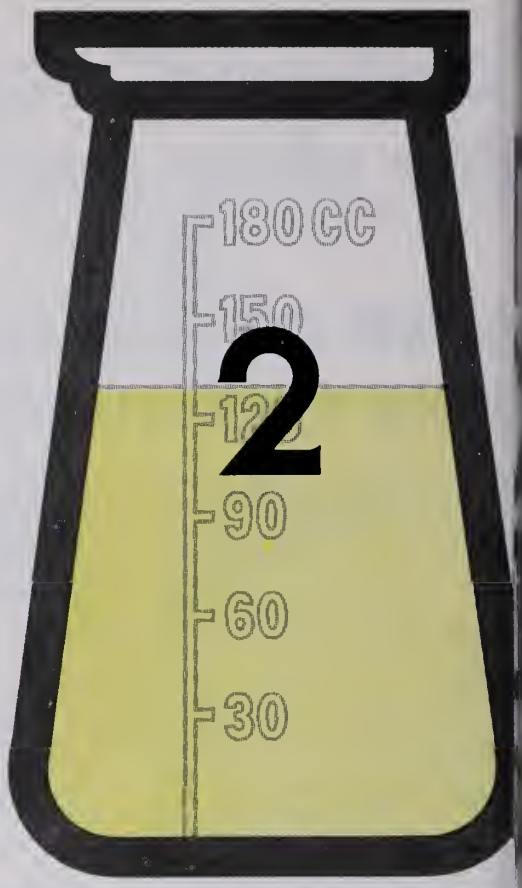
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Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

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Editorials

Sudden Infant Death Syndrome

SUDDEN DEATH of an infant that is unexpected by history and a thorough postmortem examination fails to demonstrate an adequate cause for death is called "sudden infant death syndrome" (S.I.D.S.). S.I.D.S. is estimated to cause 10,000 deaths per year in the United States. The incidence varies in different states from 1-3 cases/1000 live births. The higher incidence is noted in populations which have more people in low income brackets and more infants born with low birth weights (< 2500 gms. at term). The peak occurrence is at two to four months of age with a range of cases seen from one month to one year. Almost all deaths occur during sleep and hence, the names "crib death" or "cot death" have been used. Most cases occur in winter. About 40% of S.I.D.S. cases have a mild upper respiratory infection at the time of death.

Complete autopsy examination (including examination of the brain) reveals petechiae in the pleura, pericardium and thymus in most cases. Microscopic examination shows minimal inflammation (lymphocytes and plasma cells) in the larynx. The lungs are edematous and may contain aspirated gastric contents. In infants that are temporarily resuscitated and survive for 24 hours or more before death, associated lesions e.g. bronchopneumonia, pneumothorax etc. can be seen.

The etiology is unknown although many theories have been disproven e.g., infanticide, suffocation, poisoning, status thymicolymphaticus, hypogammaglobulinemia, hypocalcemia, and adrenal insufficiency.[1] Death caused by a single killer virus has been disproven. Research in the area of central nervous regulation of cardiorespiratory function appears promising. The observation by Steinschneider[2] that apnea and bradycardia frequently occur during sleep in apparently normal infants up to five months of age may be a clue to the final pathway in S.I.D.S. Sleep apnea is accentuated by upper respiratory infection and may correlate with the epidemiology which shows URI's in 40% of cases. The mechanism relates to an interference with adequate oxygenation through the upper respiratory tract which can accentuate sleep apnea. This results in hypoxia and death.

The psychological trauma of S.I.D.S. on family members is a major problem which has been virtually neglected. The feelings of guilt in parents, siblings, and babysitters is profound and destructive to a family unit. Parents of S.I.D.S. victims have formed local chapters to educate the public and medical profession about S.I.D.S. The local groups have been responsible for forming the National Foundation for Sudden Infant Death which is providing a forum to stimulate research and education in this area.

A basic desire of parents experiencing S.I.D.S. is for an organized system which handles this problem in a humane manner. Such a system must include identification of cases by a thorough postmortem examination, contact with families, explanation of all findings to the family, knowledge that a local parent group is available for consultation, and availability of professional counseling to the parents and siblings.

Ralph A. Franciosi, M.D.*
Minneapolis, Minnesota

*Pathologist and Director of Laboratories, Children's Health Center and Hospital, Minneapolis.

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1. Valdes-Dapena, MA: Sudden and unexpected death in infancy: A review of the world literature, 1954-1966, Pediatrics 39: 123, 1967.
2. Steinschneider, A: Prolonged apnea and the sudden infant death syndrome: Clinical and laboratory observations, Pediatrics 50: 646, 1972.

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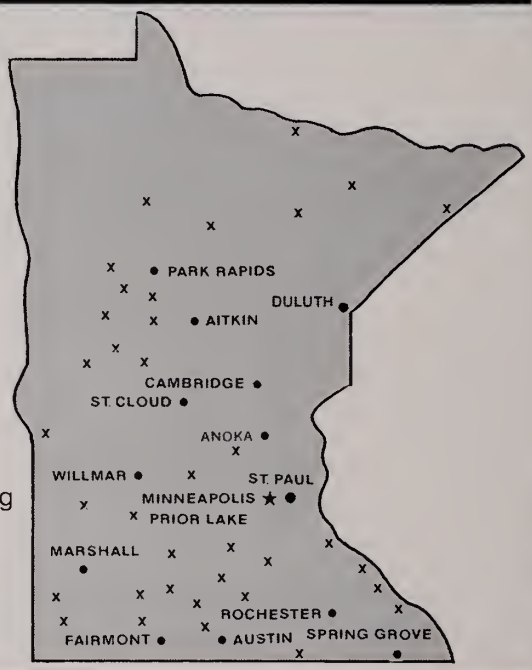
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Dextran 40 Anaphylaxis

THE ARTICLE by Krenzelok and Parker in the June issue of MINNESOTA MEDICINE* serves as an appropriate reminder that almost any substance introduced into the human body can, on occasion, produce a sensitivity reaction. Such reactions cover a wide range of severity, from minor inconvenience to severe anaphylaxis, causing death.

The dextrans are glucose polymers that result from bacterial reaction on sucrose. Dextran has probably been used most frequently clinically for its plasma expanding effects, but also for its properties of increasing blood flow in the small vessels and perfusion of tissues and for its antithrombogenic effects. Apparently, high molecular weight dextrans have been associated not infrequently with allergic reactions, but low molecular dextran, the product in current use, has proved to be relatively free of side effects. Nevertheless, as the case described by Krenzelok and Parker demonstrates, it cannot be presumed to be free of the potential for producing a serious reaction.

The most important lesson to be learned from this case, perhaps, is that the careful physician will consider every injection of a parenteral medication a possibility for producing anaphylaxis. It is imperative that he or she be prepared to administer epinephrine and appropriate supportive measures should such a reaction occur.

Robert B. Howard, M.D.
Minneapolis, Minnesota

*Dextran 40 Anaphylaxis, p. 454-455, 1974.

Presacral Dermoid Cyst

SINGLE CASE REPORTS usually do not stir medical readers. The presentation of a "Presacral Dermoid Cyst" by Dunn-Binder-Howard* surely is an exception. These authors have done an excellent job in reviewing the literature and have cited it succinctly, clearing confusion in the literature and they presented excellent classification of presacral masses.

This case report intrigues me because this patient had a huge presacral cyst, much larger than most reported in the literature. One would wonder why it had not been detected earlier in the patient's pregnancy. Also, one would wonder if the pilonidal operation performed on this lady five years previously had not been in reality removal of a postanal sinus—a frequent harbinger of a presacral cyst. This sign was pointed out by Doctors Jackman and Hawkins in their article of 1953 appearing in the American Journal of Surgery. They showed a beautiful demonstration of a sinus in the postanal space. These sinuses do not communicate with the presacral cyst, but can be confused with both pilonidal sinuses and fistulae in ano.

I would like to emphasize the malignant potential of these retrorectal masses and warn physicians that biopsies of these masses should be carried out in a transdermal approach. To do otherwise would expose the patient to seeding tumors in the rectal mucosa. The developmental presacral masses called dermoids or teratomas can develop carcinoma, but the greatest hazard is infection and repeated inflammation.

Robert J. Spencer, M.D.†
Rochester, Minnesota

*April issue, page 374, MINNESOTA MEDICINE, 1975.
†Division of Proctology, Mayo Clinic.

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Deep Tissue Infections
Suggestions for Bacteriologic Diagnosis

A SPREADING INFECTION of the deeper tissue planes complicating surgery, traumatic injury, cancer or other debilitating illness is usually cause for alarm. If gas accumulation is evident on Xray or by palpation, the prognosis is ominous A case reported by Napgezek and Hall* illustrates that what is assumed to be a clostridial gas-producing infection can be due to other pathogens, in this case Klebsiella pneumoniae.

Injury to the deeper tissues with necrosis provides an ideal environment for anaerobic bacterial metabolism. Thus, clostridia may thrive and produce the familiar gas gangrene with myonecrosis or the more benign clostridial cellulitis. Less frequently, other bacteria such as the familiar coliform may colonize under these same conditions demonstrating their facultative anaerobic capabilities. The gases (e.g. H_2, N_2) commonly produced by the clostridia and by facultative bacteria are poorly soluble in the tissue fluids and therefore tend to accumulate in the tissues.*

Bacteriologic cultures have not always been coliforms may colonize under these same condi-infections, especially when infections are mixed. These mixed infections commonly include strict anaerobic bacteria which do not tolerate exposure to air. If the specimen collection procedure or the laboratory handling of a specimen was allowed exposure to O_2, one or more bacterial species may not grow on culture, even with the best possible conditions of anaerobic incubation.

The present re-assessment of the role of anaerobic bacteria in human disease gives the physician and the bacteriologist a unique opportunity to increase the precision of clinical management as well as to promote medical progress.

The clinician, either in the operating threatre or at the bedside, must personally be involved in specimen collection. Satisfactory specimen-taking must avoid surface bacterial contamination; thus, the customary swab is anathema. The clinician concerned with possibility of anaerobic infection aims to obtain liquid specimens such as pus, effusion fluid or blood or a piece of tissue. Even these specimens may not give the desired results if they are exposed to air, delayed or allowed to dry. The best way to deliver a specimen may often be a walk to the laboratory bench, specimen in hand. It should be noted that anaerobic containers are being marketed and these should be used, especially for tissue specimens. The use of needle and syringe to aspirate a specimen is the method of choice in deep infections. If there is no liquid to aspirate, injection and re-aspiration with a small amount of sterile saline is suggested.

Having arrived in the laboratory with the specimen, the physician will communicate two phrases to the staff which should amply reward his long walk. They are "Anaerobic culture" and "Gram stain." He may want to return ten minutes later to inquire about the Gram stain findings or to examine it himself. He should then be better prepared to initiate appropriate therapy.

Without doubt, bacteriology laboratories are already experiencing the effects of the renewed interest in anaerobic infections. Even in small clinical laboratories, the majority of anaerobic bacteria can be isolated and presumptively identified. Larger centers will have to lead the way in the trial and institution of the new methodologies which are still rather expensive in technologist time and material costs.

The next decade should be an interesting one to clinicians and laboratory staff in both small and large medical centers as our experience with deep tissue infections increases. Our thanks to the authors of the stimulating case report cited.

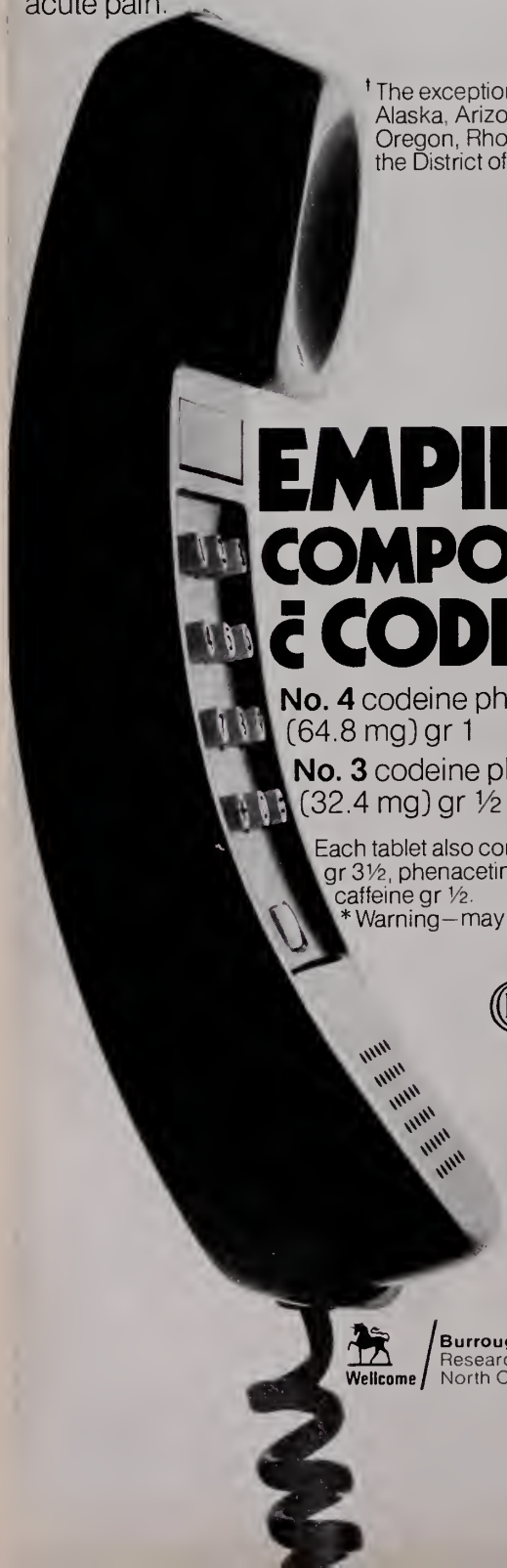
John R. Dyck, M.D.†
Minneapolis, Minnesota

*Napgezek MR and Hall WH: Nonclostridial crepitant cellulitis due to klebsiella. 58:377, 1975.
Please refer to the author's references, especially number 2
†Clinical Laboratory, Northwestern Hospital.

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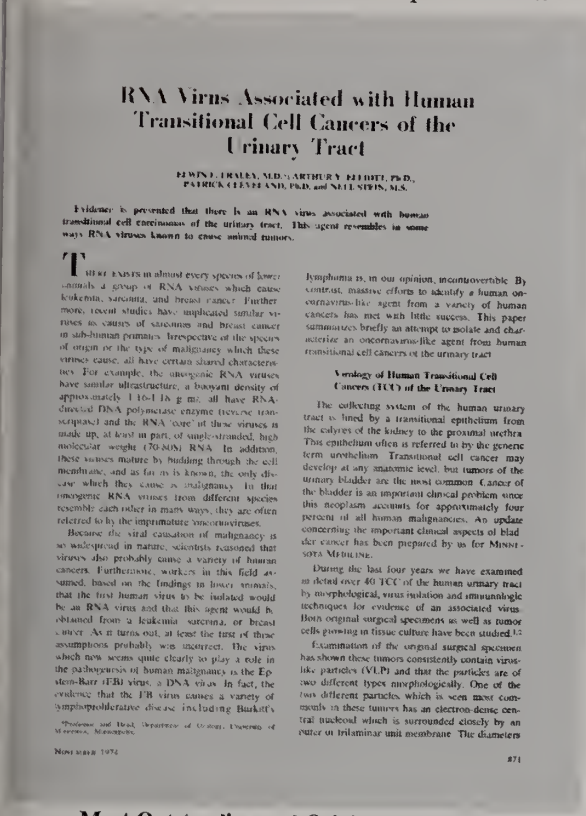
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MINNESOTA MEDICINE Honor Awards

The Board of Editors announce the following best manuscripts, best issue and best cover published in MINNESOTA MEDICINE during 1974:



RNA Virus Associated with Human Transitional Cell Cancers of the Urinary Tract

EDWIN E. FRALEY, M.D.; ARTHUR Y. ELLIOTT, Ph.D., PATRICK CLEVELAND, Ph.D. and NELL STEIN, M.S.

Evidence is presented that there is an RNA virus associated with human transitional cell carcinomas of the urinary tract. This agent resembles in some ways RNA viruses known to cause animal tumors.

THERE EXISTS in almost every species of lower animals a group of RNA viruses which cause leukemia, sarcoma, and breast cancer. Furthermore, recent studies have implicated similar viruses as causes of carcinoma and breast cancer in sub-human primates. Irrespective of the species of origin or the type of malignancy which these viruses cause, all have certain shared characteristics. For example, the oncogenic RNA viruses have similar ultrastructure, a buoyant density of approximately 1.16-1.18 g/ml, all have RNA-directed DNA polymerase enzyme (reverse transcriptase) and the RNA 'core' of these viruses is made up, at least in part, of single-stranded, high molecular weight (70-80S) RNA. In addition, these viruses mature by budding through the cell membrane, and as far as is known, the only disease which they cause is malignancy. In that oncogenic RNA viruses from different species resemble each other in many ways, they are often referred to by the imprimatute 'oncornaviruses.'

Because the viral causation of malignancy is so widespread in nature, scientists reasoned that viruses also probably cause a variety of human cancers. Furthermore, workers in this field assumed, based on the findings in lower animals, that the first human virus to be isolated would be an RNA virus and that this agent would be obtained from a leukemia, sarcoma, or breast cancer. As it turns out, at least the first of these assumptions probably was incorrect. The virus which now seems quite clearly to play a role in the pathogenesis of human malignancy is the Epstein-Barr (EB) virus, a DNA virus. In fact, the evidence that the EB virus causes a variety of lymphoproliferative disease including Burkitt's lymphoma is, in our opinion, incontrovertible. By contrast, massive efforts to identify a human oncornavirus-like agent from a variety of human cancers has met with little success. This paper summarizes briefly an attempt to isolate and characterize an oncornavirus-like agent from human transitional cell cancers of the urinary tract.

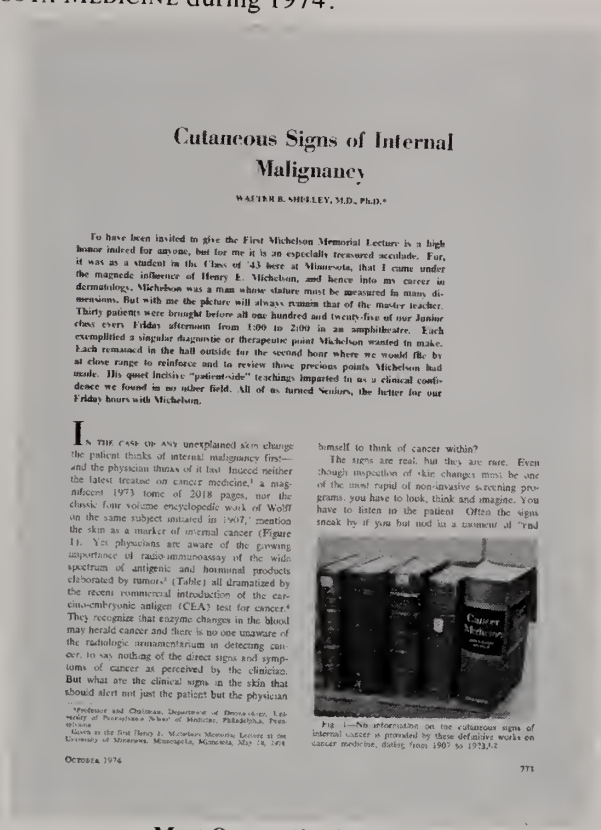
Virology of Human Transitional Cell Cancers (TCC) of the Urinary Tract

The collecting system of the human urinary tract is lined by a transitional epithelium from the calyxes of the kidney to the proximal urethra. This epithelium often is referred to by the generic term urothelium. Transitional cell cancer may develop at any anatomic level, but tumors of the urinary bladder are the most common. Cancer of the bladder is an important clinical problem since this neoplasm accounts for approximately four percent of all human malignancies. An update concerning the important clinical aspects of bladder cancer has been prepared by us for MINNESOTA MEDICINE.

During the last four years we have examined in detail over 40 TCC of the human urinary tract by morphological, virus isolation and immunologic techniques for evidence of an associated virus. Both original surgical specimens as well as tumor cells growing in tissue culture have been studied.[2]

Examination of the original surgical specimen has shown these tumors consistently contain virus-like particles (VLP) and that the particles are of two different types morphologically. One of the two different particles, which is seen most commonly in these tumors has an electron-dense central nucleoid which is surrounded closely by an outer or trilaminar unit membrane. The diameters

*Professor and Head, Department of Urology, University of Minnesota, Minneapolis.



Cutaneous Signs of Internal Malignancy

WALTER B. SHELLEY, M.D., Ph.D.*

To have been invited to give the First Michelson Memorial Lecture is a high honor indeed for anyone, but for me it is an especially treasured accolade. For, it was as a student in the Class of '43 here at Minnesota, that I came under the magnetic influence of Henry E. Michelson, and hence into my career in dermatology. Michelson was a man whose stature must be measured in many dimensions. But with me the picture will always remain that of the master teacher. Thirty patients were brought before all one hundred and twenty-five of our Junior class every Friday afternoon from 1:00 to 2:00 in an amphitheatre. Each exemplified a singular diagnostic or therapeutic point Michelson wanted to make. Each remained in the hall outside for the second hour where we would file by at close range to reinforce and to review those precious points Michelson had made. His quiet incisive "patient-side" teachings imparted in as a clinical confidence we found in no other field. All of us turned Seniors, the better for our Friday hours with Michelson.

IN THE CASE OF ANY unexplained skin change the patient thinks of internal malignancy first—and the physician thinks of it last. Indeed neither the latest treatise on cancer medicine,[1] a magnificent 1973 tome of 2018 pages, nor the classic four volume encyclopedic work of Wolff on the same subject initiated in 1907,[2] mention the skin as a marker of internal cancer (Figure 1). Yet physicians are aware of the growing importance of radio-immunoassay of the wide spectrum of antigenic and hormonal products elaborated by tumors[3] (Table) all dramatized by the recent commercial introduction of the carcinoembryonic antigen (CEA) test for cancer.[4] They recognize that enzyme changes in the blood may herald cancer and there is no one unaware of the radiologic armamentarium in detecting cancer, to say nothing of the direct signs and symptoms of cancer as perceived by the clinician. But what are the clinical signs in the skin that should alert not just the patient but the physician himself to think of cancer within?

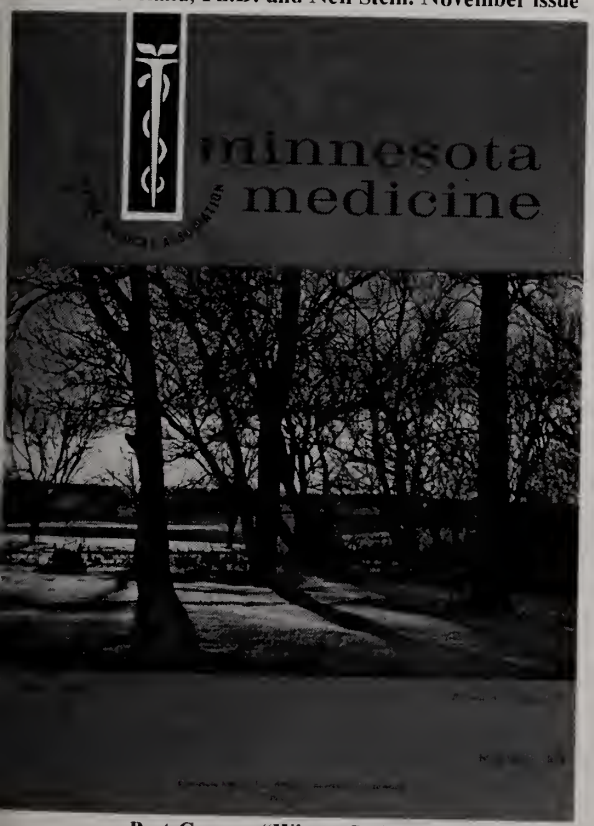
The signs are real, but they are rare. Even though inspection of skin changes must be one of the most rapid of non-invasive screening programs, you have to look, think and imagine. You have to listen to the patient. Often the signs sneak by if you but nod in a moment of "mind

Fig. 1.—No information on the cutaneous signs of internal cancer is provided by these definitive works on cancer medicine, dating from 1907 to 1973.[1,2]

*Professor and Chairman, Department of Dermatology, University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania

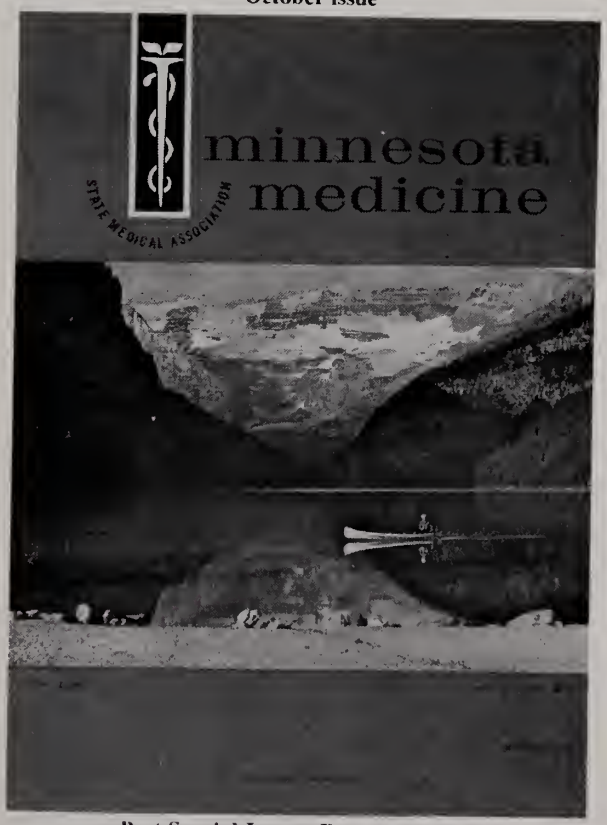
Given as the first Henry E. Michelson Memorial Lecture at the University of Minnesota, Minneapolis, Minnesota, May 14, 1974

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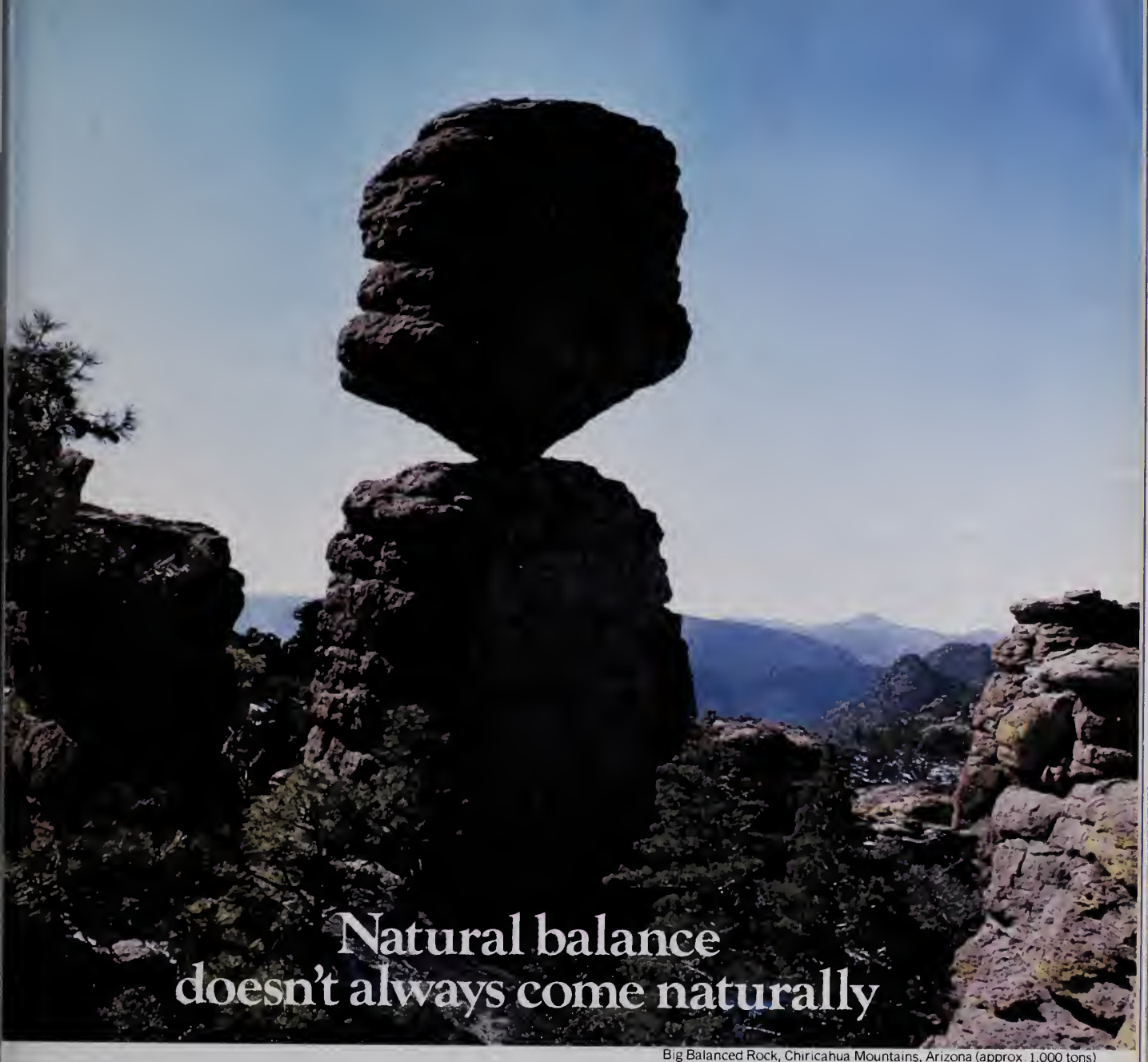
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(Continued on page 709)



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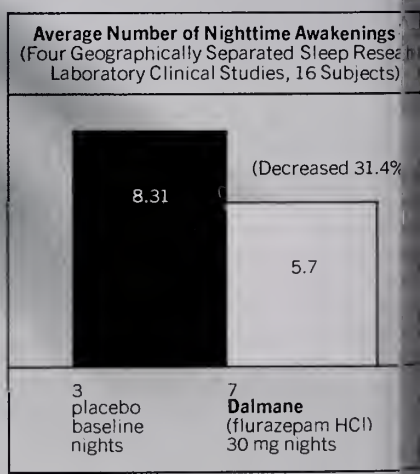
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st JD Jr: A system for automatically zing sleep. Scientific exhibit at the annual Clinical Convention of the ican Medical Association, Boston, 9-Dec 2, 1970; and at the 42nd annual ific meeting of the Aerospace Medical iation, Houston, Apr 26-29, 1971

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Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

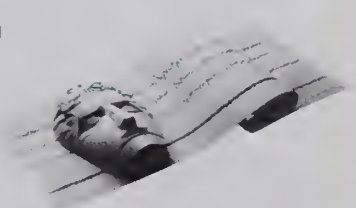
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Opinion & Dialogue

Should a specially prepared package insert be made available to patients?



Dr. Alexander M. Schmidt
Commissioner,
Food and Drug
Administration



Dr. James H. Sammons
Executive Vice President
of the American
Medical Association

The idea of a so-called pati
package insert has been aroun
a long time. Many physicians alr
use written instruction sheets tc
provide patients with informatic
about the drugs they are taking.
some physicians give verbal ins
tions; but in too many instances
these are what I call eye-glazing
ercises. I have seen patients sit
glazed eyes listening to a rapid-f
lecture by a hurried physician w
has 20 people out in his waiting
room. These patients aren't give
sufficient understanding and th
fore do not follow instructions. S
think the idea of an official pack
insert for patients is a good one.
Perhaps we should really think
this kind of information simply a
extension of drug labeling.

The benefits of patient involvem

Many physicians may not r
ize how frequently a patient obt
his drug information from Aunt
Tillie or the next door neighbor.
this information is almost alwa
bad or irrelevant to the case at h
Furthermore, the incentive to g
along with a prescribed progran
slim if the only reading matter t
patient receives, along with his
scription, is a bill.

As an educator I am impre
by the principle that the best wa
get someone to do something is
involve him in the process. So th

I think there are advantage
well as some real disadvantages
a patient package insert. When
begin to use semi-medical or m
cal terms to describe complicat
or possible sequelae of disease
treatment, you may frighten the
tient—particularly since the mo
highly sophisticated patient is n
the one who is going to read the
sert. The patient who will read it
the one most susceptible to frig
and confusion by the language.

On the positive side, a pac
insert will probably give the pat
better insight into why he is bei
treated the way he is, and it ma
give the physician a little bit mo
time. But it does not remove fro
the physician the need or obliga
to explain the insert.

Some pitfalls in the inclusion of side effects

Certainly a patient should
warned of the possibility of seri
side reactions—to know what th
real dangers are. But it doesn't
bit of good to indicate that a pat
on oral penicillin may develop a
rash, itching, or a drop in blood
pressure. Or that he may faint. I
think the real danger is that frig
engendered by the insert may p
sibly outweigh the potential goc

main purpose of drug information for the patient is to get his cooperation in following a drug regimen.

Preparation and distribution of patient drug information

We would hope to amass information from physicians, medical societies, the pharmaceutical industry and centers of medical learning. The ultimate responsibility for uniform labeling must, however, rest with the Food and Drug Administration. There is nothing wrong with this agency saying, "this information is generally agreed upon and therefore it should be used," as long as our process for getting the information is sound.

Distribution of the information is a problem. In great measure it would depend on the medication in question. For example, in the case of an injectable long-acting progesterone, we would think it mandatory to issue two separate leaflets—a short one for the patient to read before getting the first shot and a long one to take home in order to make a decision about continuing therapy. In this case, the information might be put directly on the package and not removable at all. But for a medication like an antihistamine this information might be issued separately, thus giving the physician the option of distribution. This could preserve the placebo use, etc.

It is in the distribution of patient information that the pharmacist may get involved. As professionals and members of the health-care team and as a most important source of drug information to patients, pharmacists should be responsible for keeping medical and drug records on patients. It is also logical that they should distribute drug information to them.

Realistic problems must be considered

We have to expect that the introduction of an information device will also create new problems. First, how can we communicate complex and sophisticated information to people of widely divergent socioeconomic and ethnic groups? Second, what will we say? And third, how can we counteract the negative attitude of many physicians toward any outside influence or input? Hopefully the medical profession will respond by anticipating the problems and helping to solve them. Assuming we can also solve the difficulty of communicating information to diverse groups throughout the United States, our remaining task will be the inclusion of appropriate material.

What information is appropriate?

In my opinion, technical, chemical and such types of material should not be included. And there is no point in the routine listing of side effects like nausea and vomiting which seem to apply to practically all drugs, unless it is common with the drug. However, serious side effects should be listed, as should information about a medication that is potentially risky for other reasons.

Other pertinent information might consist of drug interactions, the need for laboratory follow-up, and special storage requirements. What we want to include is information that will help increase patient compliance with the therapy.

Positive aspects of patient drug information

Labeling medication for the patient would accomplish a number of good things: the patient could be on the lookout for possible serious side effects; his compliance would increase through greater understanding; the physician would be a better source of information since he would be freer to use his time more effectively; other members of the health-care team would benefit through patient understanding and cooperation; and, finally, the physician-patient relationship would probably be enhanced by the greater understanding on the part of the patient of what the physician is doing for him.

Only the doctor can remove that fear by 20 or 30 minutes of conversation.

I'm not suggesting that we withhold any information from the patient because, first of all, it would be totally dishonest and secondly, it would defeat the very purpose of the insert. I do think that a patient on the birth control pill should know about the incidence of phlebothrombosis.

If you're going to tell a patient the incidence of serious adverse reactions, then you have to tell him that a concerned medical decision was made to use a particular medication in his situation after careful consideration of the incidence of complications or side effects.

Emotionally unstable patients pose a special problem

There are patients who, because of severe emotional problems, could not handle the information contained in a patient package insert. Yet if we are going to have a package insert at all, we just can't have two inserts. I think we might simply have to tell the families of these patients to remove the insert from the package.

Legal implications of the patient package insert

Just what effect would a patient package insert have on malpractice? We could try to avoid any legal implications by pointing out that the physician has selected a particular medication because, in his professional judgment, it is the treatment of choice. For instance, you can't tell everyone taking antihistamines not to work just because a few patients develop extreme drowsiness which can lead to accidents. And what about the very small incidence of aplastic anemia rarely associated with chloramphenicol? If, based on sensitivity studies and other criteria, we decide to employ this particular antibiotic, we do so in full knowledge of this serious potential side effect. It's not a simple problem.

How do we handle an insert for medication used for a placebo effect?

With rare exceptions, physicians no longer use medications for a placebo effect. This question does raise the issue of how a patient may react to receiving a medication without a package insert.

Preparation of the package insert

The development of the insert ought to be a joint operation between physicians, the pharmaceutical industry, the A.M.A. and the F.D.A.

I view the A.M.A.'s role as a coordinator or catalyst. It is the only organization through which the profession as a whole, irrespective of specialty, can speak. It has relatively instant access to all the medical expertise in this country. And it can bring that professional expertise together to ensure a better package insert. The A.M.A. can work in conjunction with the industry that has produced the product and which is ultimately going to supply the insert.

I don't think we should rely, or expect to rely, on legislative committees and their nonprofessional staffs to make these decisions when it is perfectly within the power of the two groups to resolve the issues in the very best American tradition—without the government forcing us to do it. I think the F.D.A. has to be involved, but I'd like them to become involved because they were asked to become involved.

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Fracture Conference

Dislocations and Fracture-Dislocations of the Elbow

JAMES P. O'HARA, M.D.*; BERNARD F. MORREY, M.D.*;
EINER W. JOHNSON, JR., M.D.† and KENNETH A. JOHNSON, M.D.†

Case 1

Dr. James P. O'Hara:

The patient is a 59-year-old woman who fell and injured her left arm. When seen in the emergency room one and a half hours later, she had a severely swollen left elbow. The neurovascular status of her left upper extremity was normal. Roentgenograms of the wrist and hand showed no abnormalities. The elbow Xrays (Figure 1) showed a posterior dislocation of the elbow but no associated fractures. Dr. Staryk, would you describe your treatment of this injury?

Dr. Steven E. Staryk:

Although there is a small possibility that the dislocation might be reduced in the emergency room with the use of parenteral analgesics, I believe that the patient will need a general anesthetic for reduction. Because the injury occurred from a hyperextension deformity and leverage of the coracoid process over the distal humerus, reproducing this deformity and distal traction should reduce the dislocation. I would then immobilize the elbow in flexion at 90° for about three weeks.

Dr. O'Hara:

That is what was done, and the final result was satisfactory (Figure 2).

*Resident in Orthopedics, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.
†Consultant, Department of Orthopedics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
Address reprint requests to: Dr. J. P. O'Hara, Section of Publications, Mayo Clinic, Rochester, MN 55901.

Fracture Conference, April 2, 1973.



Fig. 1 (Case 1). Posterior dislocation of elbow without associated fracture.



Fig. 2. (Case 1). After reduction.

Case 2

Dr. O'Hara:

The second patient is a 59-year-old woman who fell and struck her right elbow while getting off an airplane. She was seen at the emergency room 30 minutes after the injury. The neurovascular status of the extremity was normal. Xrays were obtained at that time (Figure 3). Dr. Gall, would you describe the findings?

Dr. Randall J. Gall:

There appears to be a fracture of the olecranon process as well as a comminuted fracture of the radial head. There is an associated posterior subluxation of the ulna and a dislocation of the radial head posteriorly.

Dr. O'Hara:

How would you treat this injury, Dr. Carter?

Dr. Terrence E. Carter:

The olecranon fracture will need open reduction and fixation, but initially I would attempt to reduce the dislocation and then proceed with the open surgical procedure. Because of the comminution, the radial head probably will need to be excised either at the initial operative procedure or at a later time.

Dr. William P. Cooney III:

Another possibility would be to treat the problem as has been stated but to replace the radial head with a Silastic prosthesis. I do not believe there is any convincing report favoring either one or the other procedure.

Dr. Ronald L. Linscheid:

Dr. Gall, in what position would you immobilize the elbow after closed reduction?

Dr. Gall:

The elbow probably should be in extension in order to reduce the olecranon.

Dr. Linscheid:

That is correct. You would have to have the elbow in full extension to hold the olecranon. With the posterolateral radial head dislocation, what would that then do to the radial head?

Dr. Gall:

It would seem to dislocate it more.

Dr. Linscheid:

That is also right. So it would be very difficult to treat this injury by closed reduction alone and obtain a good result.

Dr. O'Hara:

The injury was treated as described by Dr. Carter, but the radial head was excised and replaced with a Silastic prosthesis at the initial surgical procedure. At her last visit four months after injury (Figure 4), her elbow flexion ranged from 35 to 130°, and she had supination to 60° as well as pronation to 80°.

Discussion

Dr. Bernard F. Morrey:

Dislocation of the elbow is common and is the

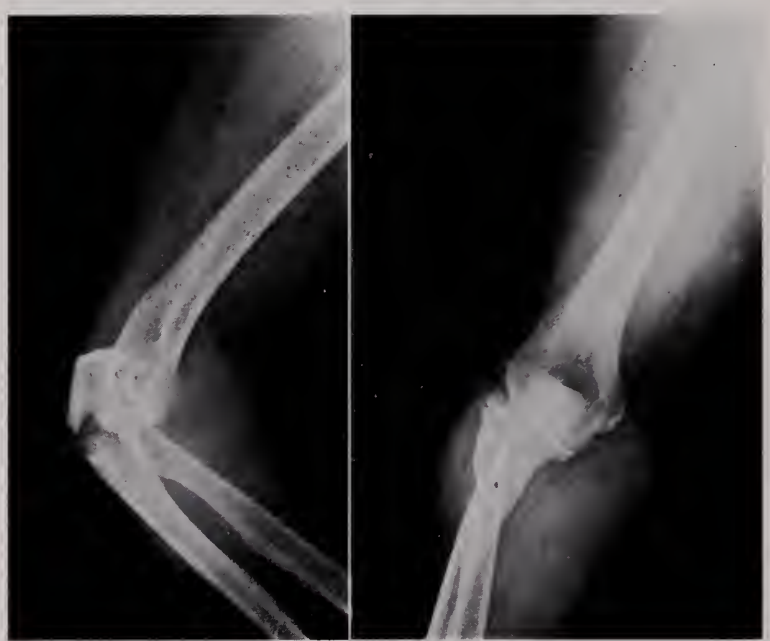


Fig. 3 (Case 2). Posterior dislocation of elbow with associated olecranon and radial head fractures.

most frequent dislocation in children less than 10 years old, yet there have only been two detailed papers on the subject in the last 20 years.[1,2] The injury occurs as a simple dislocation or one associated with fracture about the elbow; each occurs with about the same frequency. Anterior dislocations are rare and are seen in less than 1% of all elbow dislocations.

Two theories have been proposed regarding the mechanism of this injury. Loomis[3] described a fairly simple concept of hyperextension at the joint with pivoting of the olecranon in the fossa, thereby levering the humerus anteriorly through the anterior capsule and into the brachialis muscle. Sustained force drives the olecranon proximally. Osborne and Cotterill[4] suggested that the initial force occurs with the elbow in incomplete extension. The lateral sloping of the inner two-thirds of the trochlea converts vertical thrust to lateral rotation with a valgus strain, tearing the collateral medial ligament at its upper attachment. A fracture or dislocation about the wrist is seen as an additional complication in about 10% of patients with posterior dislocation of the elbow.[1]

Reduction of the dislocation should be immediate (preferably under general anesthesia), gentle, and not repetitious. A snap is often audible or sensed, resulting from the coracoid process slipping over the trochlea. The elbow is then flexed to at least 90° or as much as the swelling and the vascular status of the limb will allow. Because the edema may be considerable, a bulky compressive dressing with a posterior plaster splint is preferred during the first week. The elbow should be left at rest in a posterior splint for about three weeks. A recurrence of the dislocation is rare, usually associated with medial instability and sometimes resulting from too early mobilization. Eighty percent of recurrences occur in males, and 80% occur in children less than 15 years old.[4]

Prognosis is related to patient age, duration of time before relocation, associated fractures—especially fractures of the head or neck of the radius—and the development of myositis ossificans. In simple dislocations, 70% of patients have good results and 10%, poor results. When complicated by a fracture about the elbow, the prognosis is worse, with less than 50% of patients obtaining good results and about 30%, poor results. The importance of the patient's age is emphasized by Roberts,[2] who reported no poor outcomes in 30 patients less than 20 years old but four of 18 in patients more than 40 years old. In spite of the overall good prognosis, about 67% of all dislocations are associated with at least 10° limitation of full extension. The more severe the associated injury, the greater will be the decreased range of motion and the poorer the end result.

The most common fractures associated with



Fig. 4 (Case 2). Fixation of olecranon fracture with lag screw, and replacement of radial head with Silastic prosthesis.

dislocation of the elbow are, in order of decreasing frequency, fractures of the medial epicondyle, head and neck of radius, coracoid process, external condyle of the humerus, and capitellum. The basic principle in the treatment of fracture-dislocation consists of reduction of the dislocation and then treatment of the fracture as indicated.

Fractures of the medial epicondyle represent about 10% of all fractures of the elbow in children,[5] and almost half of these fractures are associated with dislocations of the elbow.[2,6] Of these, about 15 to 30% have the fragment incarcerated in the joint when the dislocation is reduced. Diagnosis of such a condition is made from the x-ray appearance and the development of ulnar paresthesias, because the ulnar nerve is frequently carried into the joint with the fracture fragment. Treatment is by open reduction and excision of the fragment or by fixation of the fragment with Kirschner wires. If the fragment is excised, some surgeons[6] believe that the ulnar nerve should be transferred anteriorly. Deformity will not result from excision of the medial epicondyle because this is an apophysis and does not contribute to linear growth.

The literature is replete with documentation of the poor prognosis associated with fractures of the head or neck of the radius. Dislocation is seen in about 10% of these fractures.[5,6] The reasons for the poor prognosis are the altered mechanics of the elbow joint associated with the fracture itself and the higher incidence of myositis ossificans with this injury. The treatment of choice is early excision of the radial head in the adult. In the child, the radial head must not be excised because complications arising from excision (growth arrest, cubitus valgus, and prominence of the ulna) are much worse than is a simple limitation of motion at the elbow. Linscheid and Wheeler[1] emphasized that unrecognized radial redislocations after excision of the radial head are important factors yielding poor results.

The occurrence of symptomatic myositis ossificans is a most significant factor precluding a good result with dislocation of the elbow. Myositis ossificans is seen more often after dislocation of the elbow than after any other injury, probably because of the invariable tearing of the brachialis muscle with dislocation. The cause of myositis ossificans remains an enigma. Thompson and Garcia[7] have reported a higher incidence of myositis ossificans in the older age group—50 times more frequent with an associated fracture and 70 times more frequent after a fracture of the radial head. The degree of soft tissue injury and swelling also makes myositis ossificans more likely.

The development of this condition may be suspected if the patient complains of prolonged pain and is slow in regaining a near normal range of motion. Roentgenographic evidence of calcification is seen three to four weeks after injury.

Factors such as excessive hyperextension of the elbow on reduction, repeated attempts at reduction, delay of greater than 24 hours in excising the radial head, and allowing early motion and passive exercises increase the possibility of myositis ossificans.

Resolution of myositis ossificans may be favorably altered by prolonged immobilization of up to six weeks. Surgical treatment of myositis ossificans should never be done while the process is in the proliferating stage. Even if surgical excision is done after the process has matured, the results are often disappointingly poor. Because the possibility of myositis ossificans developing with very early motion is significant, such motion is to be condemned.

Neurologic complications with dislocations are seen in three settings: (1) fracture with displacement of the medial epicondyle as previously mentioned, (2) fracture with associated vascular injury, and (3) fracture with severe soft tissue injury. As many as 20%[1] of patients will have neurologic symptoms, but these are usually transient.

Vascular compromise is not common, and when present, it is often alleviated when the dislocation has been reduced. Persistent symptoms of vascular insufficiency justify early exploration and definitive treatment.

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Laboratory Medicine

Beyond the Blood Bank

Transfusion Liability

SUSAN JARVIS, J.D.* AND BRUCE W. JARVIS, M.D.*

Is the physician who is not directly involved in blood banking free of liability resulting from a blood transfusion? Until recently, many members of the medical profession felt that they were free of any danger of liability resulting from a blood transfusion. However, recent litigation has indicated that any physician who orders a transfusion may be bringing himself into the realm of possible future liability. The most likely theory of liability that would be applicable is that of tort liability based on the theory of negligence. A major area of concern within negligence is based on the standard of care required. The answer to three questions will clarify the problem:

1. What is tort liability?
2. What is negligence?
3. How is a doctor's standard of care susceptible to negligence liability?

Tort Liability

Most medical malpractice cases are being brought under tort law. A tort is a private or civil wrong resulting from violation of a duty owed to the injured party, the plaintiff. Although some malpractice suits are now based on contract breach, most still rest on a theory of tort liability.

Negligence

Negligence is one theory of tort liability. A formula is usually applied in order to determine whether or not a member of the medical profession has been negligent in his practice. Professor Prosser of Hastings Law School developed a formula that is now recognized by many courts as establishing the four elements necessary for a finding of negligence. These elements are as follows:

1. A duty recognized by law that requires the actor to conform to a certain conduct standard in order to protect others against unreasonable risks.
2. A breach of that duty, or in other words, the actor's failure to conform to the standard mentioned above.
3. "Proximate cause," or a causal relation between the mentioned conduct and the injury suffered, and
4. An actual loss or damage sustained by the plaintiff.

The plaintiff must prove all four of these elements in order that a negligence suit be maintained. The defendant's attorney will thus attempt to prove that one or more of these elements is lacking.

Required Conduct Standard

As mentioned above, the first element in negligence is the duty of conduct that has been recognized by law. This sounds uncomplicated, and until recently it was. In the past, the "locality rule" applied. Physicians were held responsible for adhering to the standard of care observed by others in the same field of medicine in the same or similar locations. Thus, a family physician in a rural area was held responsible for observing a standard of care practiced by other family physicians in similar rural areas, whereas a doctor in an urban environment was required to practice the same standard of medicine as a doctor in a city of a similar size. This reasoning was based on the idea that rural physicians did not have the opportunity to keep abreast of the newest developments and techniques as did their peers in the cities.

A recent case in Louisiana discarded this locality rule. The court said that it did not matter that a radiologist defendant practiced the same standard of care as did other radiologists in that same community. The court used a standard based on reasonable care and skill combined with a doctor's best judgment. This case may well have started a trend toward abolishing the locality rule. In other cases, the courts have said that medical care standards are on a nation-wide basis. This would be especially true if there were questions

*New Orleans, Louisiana.

about the indications for a transfusion of a single unit of blood.

The Single Unit Transfusion

This standard of care controversy is applicable to the ordering of blood transfusions. If a doctor orders a single unit transfusion, and there is any question about the need for the blood, and the patient develops a post-transfusion hepatitis, the court may later find that the doctor was negligent in ordering the blood because he failed to exercise a standard of care that the court would find acceptable based on reasonable care, skill, and good judgment.

It is thus vital that physicians become well informed about the latest information available on transfusions. It has become apparent that transfusion liability now extends well beyond the blood bank.

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Request for Physician's Art Work

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Although in the past we have printed cover pictures depicting many distant part of the world, photographs of life in Minnesota will be given preference. Pictures will be returned if identified with the name and address of the physician. Please submit your picture as prospective cover subjects to the Editor of MINNESOTA MEDICINE, 375 Jackson St., St. Paul, Minnesota 55101.

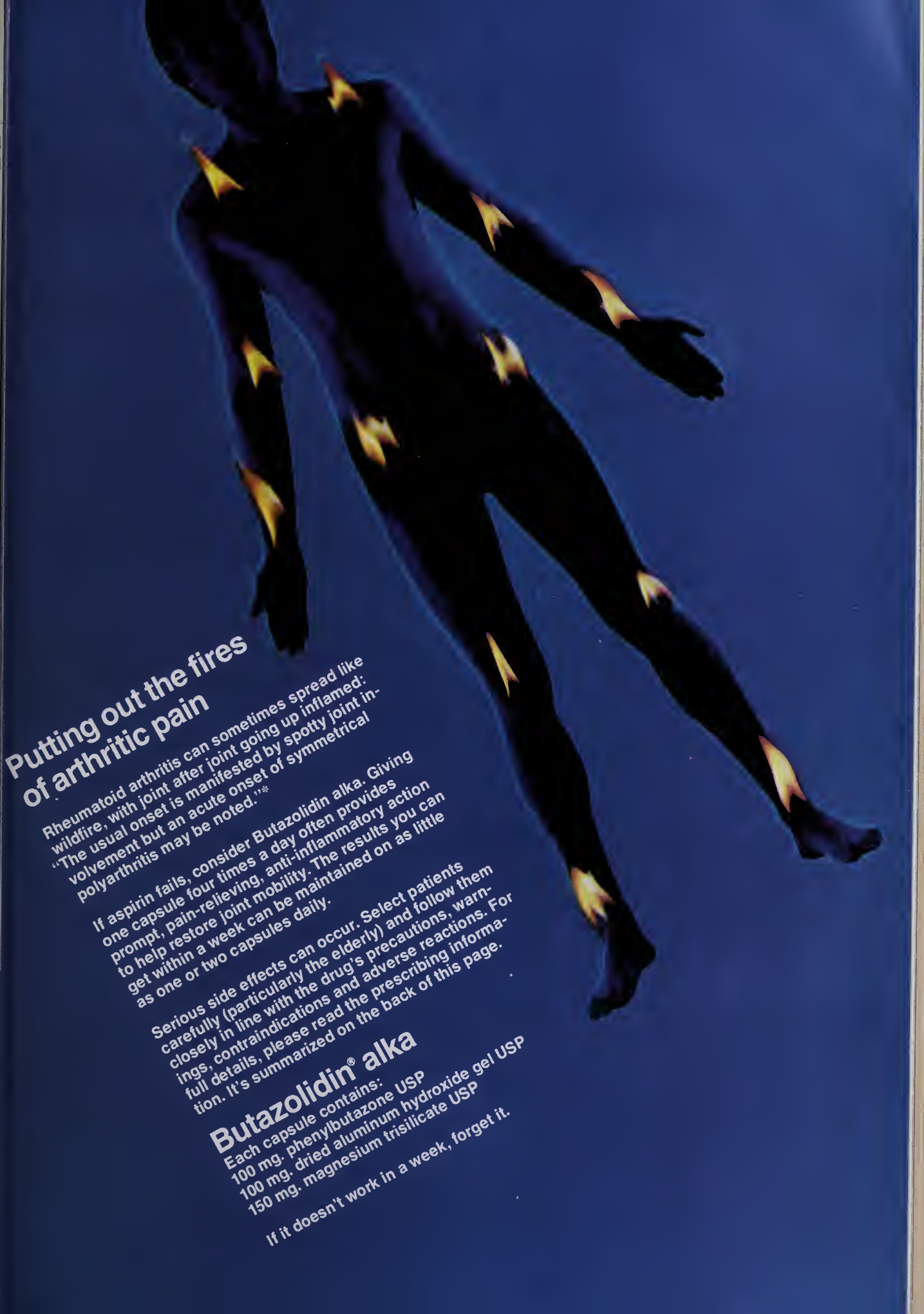
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Farrell Stiegler, M.D.
Cover Editor

Letters to the Editor

We would like to encourage physicians to contribute to the Letters to the Editor Section. We want to hear what you have to say, what you think, why you hold certain opinions. In short, we want to make this as lively and spirited a section as possible.

The Editors



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If it doesn't work in a week, forget it.

Ragan, C.: The Clinical Picture of Rheumatoid Arthritis, in Arthritis, ed. 8, edited by J. L. Hollander and D. J. McCarty, Jr., Philadelphia, Lea & Febiger, 1972, chap. 21, p. 335.

Geigy

Important Note: This drug is not a simple analgesic. Do not administer casually. Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter. Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently. Warn patients not to exceed recommended dosage. Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy. Dosage should be taken with meals or a full glass of milk. Substitute alka capsules for tablets if dyspeptic symptoms occur. Patients should discontinue the drug and report immediately any sign of fever, sore throat, oral lesions (symptoms of blood dyscrasia); dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema. A one-week trial period is adequate. Discontinue in the absence of a favorable response. Restrict treatment periods to one week in patients over sixty.
Indications: Rheumatoid arthritis, osteoarthritis, bursitis, acute gouty arthritis and rheumatoid spondylitis.
Contraindications: Children 14 years or less; senile patients; history or symptoms of G.I. inflammation or ulceration including severe, recurrent or persistent dyspepsia; history or presence of drug allergy; blood dyscrasias; renal, hepatic or cardiac dysfunction; hypertension; thyroid disease; systemic edema; stomatitis and salivary gland enlargement due to the drug; polymyalgia rheumatica and temporal arteritis; patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy.
Warnings: Age, weight, dosage, duration of therapy, existance of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.
Precautions: The following should be accomplished at regular intervals: Careful detailed history for disease being treated and detection of earliest signs of adverse reactions; complete physical examination including check of patient's weight, complete weekly (especially for the aging) or an every two week blood check; pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.
Adverse Reactions: This is a potent drug; its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy; CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia; ulcerative stomatitis, salivary gland enlargement.
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History

Dr. Burnside Foster (1861-1917)

Dermatologist, Medical Journalist, Medico-Historian

ROBERT ROSENTHAL, M.D.

Dr. Burnside Foster, who was to become one of Minnesota's outstanding physicians, arrived in Minnesota near the end of 1887 from New England.

Dr. Foster was born May 7th, 1861, in Worcester, Massachusetts. He received his preliminary education at the Boston Latin School and the Hopkinson Boys School at Boston. Then he attended Andover Academy and from there went on to receive a good classical education at Yale, where he earned his B.A. in 1882. Foster received his medical education at Harvard Medical School, where he was given his M.D. degree in 1885. Following an Internship at the Massachusetts General Hospital, he took a trip to Europe where he visited medical schools in Dublin and Vienna. In Vienna, he was impressed by the excellent Department of Dermatology of the University Medical School and there decided to specialize in this field which, of course, at that time included the diagnosis and treatment of venereal diseases.

It is no surprise that he excelled in his studies if one looks at his background. He was a seventh-generation New Englander. The first Fosters had come to Ipswich, Massachusetts, in 1683. His great-great-grandfather, Dr. Thaddeus Maccarty, was a New England country doctor, who was born in 1747, finished his medical studies in 1770, and who commenced medical practice the same year. Maccarty's son-in-law, John W. Stiles of Worcester, Massachusetts, in 1836 wrote a biographic sketch of him, but did not publish it. That was left to his great-great-grandson, Dr. Foster.* His father, Dwight Foster, was a judge on the Massachusetts Supreme Court. His mother, Henrietta Perkins Baldwin also had at least one distinguished ancestor: Her father, Sherman Baldwin of New Haven was governor of Connecticut and a United States senator.

As mentioned, Foster came to Minnesota late in 1887 and began to practice in Minneapolis the following year. He lived in his office, using a desk that was converted into a bed. In his dermatological practice he was associated with another physician—probably Dr. Max P. Vander Horck.† Very soon Foster was appointed Assistant Professor in Anatomy at the University of Minnesota.

In 1891, Dr. Foster had established himself in St. Paul, apparently taking over the office of Dr. LeGrand N. Denslow‡ when the latter moved away; however, according to his family, Foster chose St. Paul because of the "higher standards" of the medical practice there. From this time on he limited his practice to his specialty—Dermatology and Venerology.

Foster became a member of the Ramsey County Medical Society in 1891, the year he came to St. Paul. Being a very active member, he became its secretary in 1897, vice president in 1905, and president in January 1906. He read many interesting papers, pertaining to his specialty, at the Society's meetings.

In 1899, Dr. Foster was appointed Clinical Professor of Dermatology at the University and held this position for many years. Being an outstanding practitioner, he soon was elected Dermatological Consultant to St. Joseph's Hospital, St. Luke's, and Bethesda Hospitals. He also was the first president of the Minnesota Dermatological Society.

One of the most important events in his medical career was his association with the St. Paul Medical Journal, when it was founded in 1898. He was its editor from the beginning until January 1, 1916—that is, for eighteen years. To this journal he contributed not only his journalis-

*Dr. Foster edited and published this biographic sketch in the Boston Medical and Surgical Journal, 148, 301-305, 1903, under the title, "An Account of Thaddeus Maccarty, a New England Country Doctor of Pre-revolutionary Days." The reprint is a pamphlet of 17 pages.

†Dr. Max Posa Vander Horck, 1862-1911. Professor of Dermatology and Genito-Urinary Diseases at the University of Minnesota since 1888. He was associated with Dr. F. A. Dunsmore until 1889 and then practiced alone.

‡Dr LeGrand N. Denslow, born 1852, died after 1912. He specialized in skin diseases and genito-urinary diseases. He came to St. Paul from Minneapolis in 1885 and left St. Paul about 1890; he later practiced in Los Angeles.

tic leadership but also many articles and a tremendous number of reviews of books and articles. In 1900, he wrote 24 book reviews in seven months. The editing and publishing committee at the time of his retirement stated, "His scholarly editorials, written in his finished style and faultless English, will undoubtedly be missed. The editorial pages of the Journal have repeatedly exerted the most widespread influence. Dr. Foster was the first to urge the frequent examination of people in apparently good health that they might be guided by their physicians in the preservation of their most valuable asset." In recognition of his services in this area of medicine he was named a member of the Board of Trustees of the Life Extension Institute of New York. He also was medical examiner for the New England Mutual Life, the Equitable Life, and Home Life Insurance companies. In 1909, he was invited to address the Association of Life Insurance Presidents in New York on methods of increasing the life span of their policy holders.

In an editorial he attacked the immoral medical advertisements in the daily papers. As a result, the Postmaster General of the United States ordered the exclusion of papers carrying such advertisements from the United States mails. More than once Foster used strong words against the practice of fee splitting—always being motivated by medical ethics. When editorializing against euthanasia, he upheld the right of an individual to live his life.

Under his leadership—states his contemporary, Dr. H. Longstreet Taylor—the ST. PAUL MEDICAL JOURNAL had "the unique distinction of being the only organ of a county medical society that survived the diseases of infancy.*" In recognition of his excellence as a medical editor, Foster was elected vice-president of the American Medical Editor's Association at its meeting in St. Paul in June 1901. His competent editorship and business acumen were also a boon for the Ramsey County Medical Society because, from time to time, surplus funds were transferred to the Society's Building and Library Fund.

As editor of a medical journal Foster was, of course, interested in the entire field of medicine and the welfare of the medical profession. It is not surprising that he was annoyed by the following: A hall of fame was to be erected under the directorship of the University of New York, and lists for prospective individuals to be selected for inclusion were invited. Among 750 lists of 50 names each not a single physician was proposed. Foster gave vent to his anger in verse entitled "The Doctor at the Parting of the Centuries—A Poem," which was published in the ST. PAUL MEDICAL JOURNAL in 1900.†

Dr. Foster and the editor of the JOURNAL LANCET were intimately acquainted while Foster lived in Minneapolis, and the friendship between the two editors continued after he moved to St. Paul, although at times the two differed over editorial opinion and policy. Foster's editorials often were referred to in a most complimentary manner, and he was recognized as an authority and as "a clear and clean cut writer" who had mastered his subject matter.

In his specialty, Foster was an outstanding teacher and consultant. He remained connected with the University of Minnesota in the Department of Dermatology until his death. That he was dermatological consultant to practically all St. Paul hospitals has been stated; he also was surgeon to the skin and venereal department of the City and County Hospital of St. Paul, and he was visiting physician to the St. Paul Free Dispensary. After Vander Horck's death in 1911 Foster continued to teach at the St. Paul Dispensary, assisted by some of St. Paul's pioneer dermatologists: at first by Dr. Charles Freeman, Sr. and later by Drs. John Armstrong and Henry (Nick) Klein. He was a member of the American Dermatological Association and the first president of the Minnesota Dermatological Society. Paul E. Bechet in his biographical sketch of Foster‡ tells the story that when the latter was asked for a list of his papers the reply was "too numerous and not of sufficient importance to chronicle."

Dr. Foster excelled in three fields: We wrote of him as an accomplished medical journalist and an outstanding specialist in Dermatology. The third field was that of History of Medcine. He was one of the earliest teachers of this subject in the United State# and probably the first in the State of Min-

*H. Longstreet Taylor, in American Medical Biographies: "Burnside Foster (1861-1917)" Boston Medical and Surgical Journal 180:277. 1919.

†St. Paul Medical Journal 584-5, 1900. It was read at the Third Annual Meeting of the Minnesota State Medical Society in Duluth.

‡Paul E. Bechet, "A History of the American Dermatological Association" in commemoration of its 75th Anniversary, 1876-1951, Froben Press, 1952, p. 149.

#George Rosen: History in Medical Education in Ciba Symposia, Summer 1951, p. 1364.

nesota. His lectures must have been of unusual excellence and most stimulating, judging from his "History of Medicine and the Medical Profession," which he himself termed "Extracts from a course of lectures delivered before the students of the University of Minnesota during the winter of 1898." This history was published serially in THE JOURNAL LANCET in 13 issues from May to November 1898. His clear style and his tremendous knowledge of the subject make it delightful reading. His interest in this field of medicine is shown also by other publications or papers, including "The Bubo Plague in China, with a brief account of the Great Plague in London" and "William and John Hunter and the Medicine of their time." He presented many papers dealing with historical subjects. Among these were "A Brief History of the Origin and Practice of Mutilating Operations on the Sexual Organs" (1897), "William and John Hunter and their influence at the end of the 18th century" (1900), "Edward Jenner and Smallpox" (1901), "A Sketch of John Abernathy" (1904), and "Sir Joseph Lister" (1912). That he published many articles on dermatological subjects is to be expected. Many of these appeared in the JOURNAL OF CUTANEOUS DISEASES from 1894 to 1916.

It seems Foster loved to attend medical congresses, and he very often presented papers or discussed papers of others. He apparently was much interested in the development of the Federal Food and Drug Laws.

An editor and writer of his caliber must have been a great reader. Charles Dickens and Francis Trollope were two of his favorite authors. He loved poetry and was very fond of the older authors and the works of the less known classical writers. His library contained Mark Twain's autobiography.

On New Year's Day, 1894, he married Sophia Vernon Hammond, a daughter of General John H. Hammond, who had served in the Civil War. Dr. Foster was a confirmed family man. He had three children: A son, Roger, of Washington, D.C.; a daughter, Elizabeth (Mrs. Vitracyl), of Sparkhill, New York; and a daughter Harriet (Mrs. Bunn), of Madison, Wisconsin, who with his wife survived him. He excelled in all social virtues, and his family and his home were his most highly prized possessions. He was considered to be a perfect host and a gourmet. In summertime, he worked only on alternate days in his office. He early recognized the refreshing influence of a country house in summer, and as early as 1900 he owned one in Osceola, Wisconsin, and thereby hangs a tale. It was at about this time that the following incident took place. Foster took the train from St. Paul to Wyoming, Minnesota, arriving there about one o'clock in the morning. He awakened two boys whom he found sleeping in a restaurant and offered them a good fee for driving him to his summerhouse. This offer, and perhaps the fact that he carried a considerable amount of money, apparently was overheard because the restaurant was soon held up by three men. Being particularly afraid he might lose his father's watch that he carried, Foster put down his cigar and objected vigorously. In the ensuing struggle he used a flat iron which he discovered near him. The robbers killed the two boys whom Foster had tried to hire and was himself knocked unconscious. When people from the neighborhood found him, they assumed that Foster had killed the boys, and they apparently tried to lynch him. However, a farmer who had been a patient of Foster's for some dermatological condition of his hands recognized him. Foster was saved. The bandits were caught later and one of them received the death sentence. This convict invited the doctor to the hanging—an invitation which was not accepted. His skull was left to Dr. Foster.*

Later (about 1909) Foster acquired a new site for a summerhouse—at Otisville on the St. Croix River—being one of the first to settle there on the river. He loved the outdoors, was an enthusiastic fisherman,† but his hunting career was very short. After killing a deer, he turned against hunting and sold his guns.

Dr. Foster kept up with the latest medical literature. His medical articles are of an excellent caliber, and he was a fine diagnostician and able therapeutist. He was a cautious and considerate physician. His "caution and yet perspective outlook is shown in his paper on x-ray therapy."‡

*Letter from Dr. Francis Lynch, St. Paul, dated November 15, 1952

†His library contained a facsimile edition of the first edition of Izaak Walton's, "The Complete Angler."

‡Lawrence Charles Parish, Biographica Dermatologica "Burnside Foster," in Cutis 5 (3), March, 1969 320-322 (port). It contains lengthy quotations from Foster's writings. The article on x-ray therapy is "The present stage of our knowledge concerning the therapeutic value of the Xray," a paper read at the annual State Medical Society Meeting in 1905; published in the Journal of the Minnesota Medical Association and Northwestern Lancet 26, 1906, 23-26.

Successful in practice, journalism, teaching, and lecturing he still remained a modest man. He was, as one of his biographers put it, "energetic, vigorous, a lover of truth, a firm friend, an implacable foe of all that was false, and withal a courteous gentleman." We can add that he was one of the most important members of the medical profession in this area and especially of the Ramsey County Medical Society.

Dr. Foster died at his St. Paul home at 117 Farrington on June 13, 1917, in his 57th year. The cause of death supposedly was a brain tumor.* He did have some naevus during his final illness, which he treated himself and for which he consulted physicians in Boston, but this was not considered to be connected with his final illness. He was buried in Forest Cemetery.

There is an old European adage, "Tell me with whom you associate and I shall tell you who you are." One wonders if in a similar way one could ask, "Let me see your library and I shall tell you what kind of scholar you are." The writer of this biographical sketch has tried to round up as many titles of Foster's books as it was possible.† It seems that his library was kept fairly intact until the death of his widow in 1952.‡ The legal books, no doubt, belonged to his brother.

There is no doubt but that a considerable portion of his library must have been dispersed, especially books dealing with Dermatology and Venerology. It is fair to assume also that he acquired many books to review from publishers and others because he was editor of the ST. PAUL MEDICAL JOURNAL.

St. Paul was fortunate to have a medical man of his caliber and the Ramsey County Medical Society had in him one of the finest and most influential supporters.

*This is the diagnosis given on this death certificate, signed by Dr. Arthur Sweeney, neurologist of St. Paul. The tumor supposedly had been present for about six months.

†Of journals there was the JOURNAL DE MEDICINE, CHIRURGIE ET PHARMACI, 1783. Two volumes of the Transactions of the Minnesota State Medical Society (1891 and 1893). No doubt there must have been many more, but they probably were disposed of after his death.

History of Medicine was well represented: James Thatcher: "American Biography, or Memories of Eminent Physicians who have Flourished in America," 2 volumes, Boston, 1828. A number of volumes from "Masters of Medicine" (1898); Henry Gordon: **Sir James Young Simpson and Chloroform;** D'Arcy Power: **William Harvey;** Julius Leopold Pagel: **John Hunter;** William Stokes: **Sir William Stokes;** Timothy Holmes: **Sir Benjamin Collins Brodie;** Heinrich Haeser: **Ubersicht der Geschichte der Chirurgie und des Chirurgischen Standes,** Stuttgart, 1879. Clifford Howard: **Sex Worship,** Washington, D.C., 1898. William Sedgewick Saunders: **Sketches from the History of Medicine—Ancient and Modern.** Oration of the Huntarian Society, 1867. (Private circulation 1808). Valery Radot: **Louis Pasteur, His Life and Labors,** translated by Lady C. Hamilton, New York, 1885. **Syphilis in Ancient and Prehistoric Times.** Robley Dunglison: **History of Medicine from the Earliest Age to the Commencement of the Nineteenth Century,** arranged and edited by his son, Dr. Richard J. Dunglison, Philadelphia, 1873. Alfred C. Garratt: **Myths in Medicine and Old Time Doctors,** New York, London, 1884.

Of course, there were numerous articles on Medico-historical Subjects, some of them in a volume. Among these was Pierre Vidor Renouard: **History of Medicine from its Origin in the Nineteenth Century,** Cincinnati, 1856.

There were a number of 18th century medical works, including John Hunter: **Treatise on the Venereal Disease;** a volume on the **Evidence of Efficiency of Dr. Perkins Patent Metallic Instruments,** (London 1797); William Cullen: **First Lines of the Practice of Physic,** Edinburgh, 1789; and also an 18th century Pharmacopoea, a Volume on Mederia Medica, etc.

Of course there were later works, especially a number of Charles Darwin's works. I also want to mention Fredrick Esmarch's, **The Surgeon's Handhook on the Treatment of Wounded in the War** (English translation by H. H. Clinton, New York, 1878).

‡When Mrs. Foster died, late in 1952, it was in the Foster house that a bundle of manuscript notes were discovered in an old desk that had belonged to her father, General Hammond. These notes were part of the original field notes of William Clark of the Lewis and Clark expedition. 1803-1804.

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(Continued from page 690.)

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(Continued to page 712.)

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The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

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Contraindications: Patients with known hypersensitivity to the drug.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in fre and/or severity of grand mal seizur require increased dosage of standa convulsant medication; abrupt with may be associated with temporary i crease in frequency and/or severity seizures. Advise against simultaneo gestion of alcohol and other CNS de sants. Withdrawal symptoms (simil those with barbiturates and alcohol occurred following abrupt discontir (convulsions, tremor, abdominal ar cle cramps, vomiting and sweating) addiction-prone individuals under c

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illance because of their predisposi- o habituation and dependence. In ancy, lactation or women of child- ng age, weigh potential benefit st possible hazard.

utions: If combined with other psy- opics or anticonvulsants, consider ully pharmacology of agents em- d; drugs such as phenothiazines, tics, barbiturates, MAO inhibitors ther antidepressants may potentiate tion. Usual precautions indicated in nts severely depressed, or with latent ssion, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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President's Letter



Bureaucracy and Regulations

ON THE OCCASION of our approaching Bicentennial year, every American should take time to reflect on what has happened to our government in Washington, D.C. It is disturbing and even frightening to note that in recent years a rapidly growing and now huge top-heavy bureaucracy has been established. This bureaucracy is everywhere in the executive and legislative branches of government—it staffs the offices, committees, councils, agencies, bureaus, and departments—it drafts laws, develops position papers, and writes speeches for our congressmen—and most disturbing, it writes the rules and regulations that implement the laws and interprets the intent of the congress in passing the laws! Where does the real power of government rest?

We have become a society dependent upon experts, legitimate or self styled. Our legislators understandably feel they need more and more expert staff to advise them in our increasingly complex society how to cope with the problems presented by other experts—and bureaucracy and regulation grows. The staff expert is most often young, aggressive, personable, intelligent, and articulate. Yet these same bureaucratic experts who write the rules and regulations for the laws as employees of bureaus, agencies, and departments are likely to have other attributes as well—strong bias, power consciousness, little or no experience, and strong idealism with an axe to grind. But above all they have no public accountability! The self styled expert in health planning, consumer advocacy, and social planning must be heard but I strongly believe he has no role in the drafting of rules and regulations of the law.

It is encouraging that a prominent U.S. Representative has indicated his committee will review all health legislation passed in the past few years to see where HEW in writing regulations to implement laws has "written new law, perverted the law, or carried out the law as written". In addition, legislation was introduced in the Senate to attempt to curb the lawmaking practices of governmental agencies and departments with the hope that rule by bureaucratic edict will cease. If you agree, make your position known to your legislators at both the state and national level.

G. Roy Diessner, M.D.
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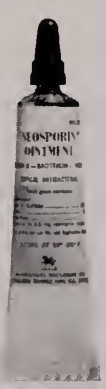
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Editor's Notebook

First the Bad News

THANKS TO ROY DIESSNER'S last two President's Letters, MINNESOTA MEDICINE has been in and out of the news lately.

We were in the news in August with Roy's editorial: "Unreasonable Expectations." If you will recall, he said television medical shows, such as those starring Marcus Welby and Joe Gannon, may cause patients to expect too much. As you know, these two mythical surefooted, surehanded, and sureminded medical heros can treat and diagnose with aplomb anything inside or outside their office or specialty. Maybe, Roy suggested, people viewing these medical supermen expect miracles from their physicians. And maybe this dissatisfaction with reality leads to an occasional malpractice suit.

The MINNEAPOLIS STAR picked up the Diessner editorial. In its August 14 edition the paper splashed this headline across its first page: "Real Doctor Finds TV Shows a Pain." Three days later, the ST. PAUL SUNDAY PIONEER PRESS had its say. The Editor of that paper, William G. Sumner, asked in his title: "So What's Wrong with TV House Calls?" In late August, United Press and Associated Press caught wind of the Diessner story and dispatched it across the land.

I do not have any quibble about how the local papers handled the story. Although the STAR's headline made me wince, the reporter presented a balanced, thoughtful analysis, and only after talking to Roy on the phone. Sumner, despite a dig at doctors for their "almost conspiratorial silence in cases of genuine malpractice", simply used Roy's editorial as a springboard for a tongue-in-cheek defense of Marcus Welby et al. To give you the flavor of his piece, here is his last paragraph: "I wish people would leave television alone. I like violence, medical shows, sports and Star Trek. What else is there?"

But I do have a small complaint about the media's handling, or nonhandling, of Roy's second Letter "Frustration", which appeared in September. His Letter says he is frustrated that the news media does not emphasize the good news about Medicine. He cites a May 1975 *Mid-Continent* Survey of 998 Minnesota Adults. The survey covered health care quality, costs, and accessibility. Of those surveyed 76 percent felt their care was good or very good, 15 percent said it was all right, and only six percent considered it bad. A Twin City metropolitan paper reported on the survey, but buried it deep in the paper and gave it only 17 lines. Surely, said Roy, Minnesotans' satisfaction with their health care deserves more coverage than that.

Apparently not. Because MINNESOTA MEDICINE has been prominently *out* of the news since Roy's second editorial. Perhaps the media's lack of comment makes his point—that the media ignores the good news about Medicine.

Roy Diessner is not the only one to complain. I invite you to read an article by Harry Schwartz, who has written extensively for the NEW YORK TIMES, in the July 1975 ARCHIVES OF INTERNAL MEDICINE.[1] In his article, appropriately called "Whatever Happened to the 'National Health Care Crisis'?", Schwartz says the media underplays news that challenges the wisdom of National Health Insurance, that questions the very existence of a "crisis", or that says something good about our present system.

Yet there is good news about American Medicine. And the people, as indicated by the Minnesota survey and a similar one in Washington, D.C. in the March 18, 1974 WASHINGTON POST, are mostly—though not completely—satisfied with their health care.

The reasons the American people are satisfied, as set forth by Schwartz, are these:

1. Health care is widely available, and most Americans have access to it.
2. The technical and scientific level of American Medicine is high, perhaps the highest in the world.
3. Most Americans—but not enough yet—are adequately protected against financial costs of illness.
4. The current system is pluralistic enough so Americans have free choices—where and how they want to receive their care—prepaid plans, fee-for-service, Veteran's hospitals, Union-sponsored clinics, public health clinics, hospital emergency and outpatient clinics, or free clinics.
5. Current data shows American medicine is doing a good job, with an almost 50 percent drop in infant mortality since 1965, and falls of 15 percent for heart disease and 77 percent for kidney disease these last 20 years.

This good news does not mean American Medicine is perfect. It is not. Nor does it mean that certain fundamental changes are not going to occur in our system. These changes will occur. Indeed, according to Elliot Richardson, former HEW Secretary and now Ambassador to Great Britain, the changes are already taking place. Richardson believes the fundamental issues of Health Care Insurance already have been resolved, and the fundamental compromises have already been struck.[2] In other words, we will have National Health Care Insurance, but it will be in continuity with our present system. What is happening is this: Because the people believe the good things about American Medicine, our country is experiencing a Health Care Evolution, towards a just, pluralistic, mixed system with protection for all; not a Health Care Revolution, with a dehumanizing central bureaucracy, with more concern for policies than people.

Richard L Reece MD

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Ragan, C.: The Clinical Picture of Rheumatoid Arthritis, in Arthritis, ed. 8, edited by J. L. Hollander and D. J. McCarty, Jr., Philadelphia, Lea & Febiger, 1972, chap. 21, p. 335.

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Warnings: Age, weight, dosage, duration of therapy, existance of concomitant diseases and concurrent potent chemotherapy affect incidence of toxic reactions. Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug. Use lowest effective dosage. Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions. The disease condition itself is unaltered by the drug. Use with caution in first trimester of pregnancy and in nursing mothers. Drug may appear in cord blood and breast milk. Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug. Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation. Unexplained bleeding involving CNS, adrenals, and G.I. tract has occurred. The drug may potentiate action of insulin, sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid). Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination. Swelling of ankles or face in patients under sixty may be prevented by reducing dosage. If edema occurs in patients over sixty, discontinue drug.

Precautions: The following should be accomplished at regular intervals. Careful detailed history for disease being treated and detection of earliest signs of adverse reactions, complete physical examination including check of patient's weight, complete weekly (especially for the aging) or an every two week blood check, pertinent laboratory studies. Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc. Cases of leukemia have been reported in patients with a history of short- and long-term therapy. The majority of these patients were over forty. Remember that arthritic-type pains can be the presenting symptom of leukemia.

Adverse Reactions: This is a potent drug, its misuse can lead to serious results. Review detailed information before beginning therapy. Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G.I. bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G.I. bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia, bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia, toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug), proteinuria, hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states, lethargy, CNS reactions associated with overdosage, including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia, ulcerative stomatitis, salivary gland enlargement.

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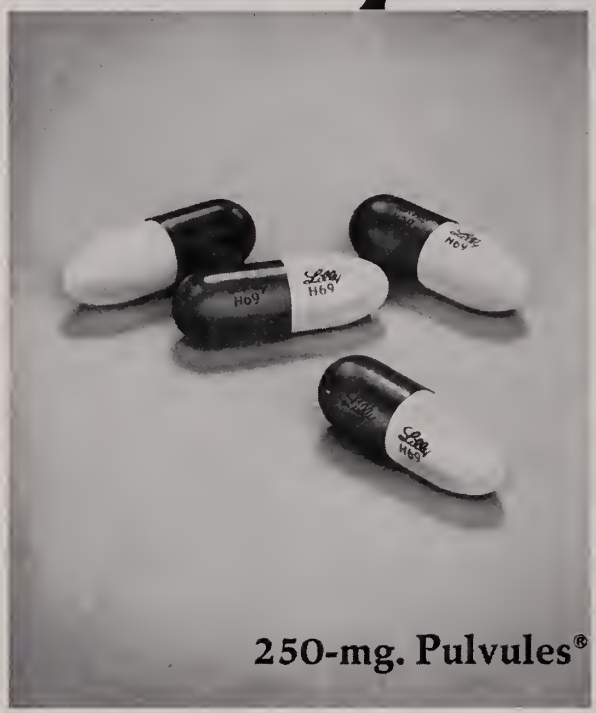
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Puzzling Pacemaker Problems

DAVID A. BERMAN, M.D.*

Here are six examples of what can happen when a cardiac pacemaker malfunctions.

PACEMAKER MALFUNCTIONS may be due to electrical problems as in battery failure or to mechanical difficulties such as recoil of the catheter lead into the right atrium. The following are examples of various kinds of pacemaker dysfunction:

Case Reports

Case 1

A 73-year-old woman complained of intermittent dizziness. Electrocardiogram showed shifting atrial pacemaker between the sinus node and an A-V junctional pacemaker. A 12-hour Holter(T) monitor revealed episodes of prolonged asystole up to six seconds duration (Figure 1). Permanent

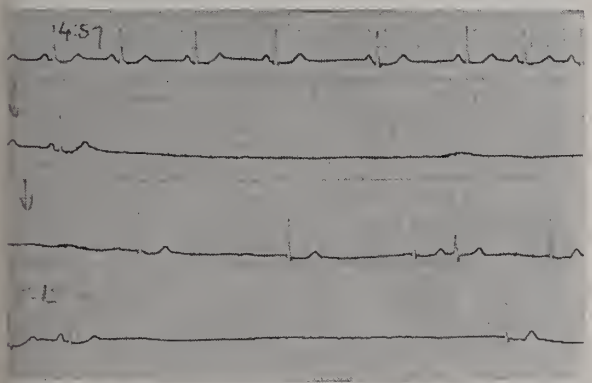


Fig. 1—Case 1—Rhythm strips from Holter(T) monitor showing prolonged asystole and junctional escape rhythm.

demand pacemaker was inserted with the electrode catheter positioned at the apex of the right ventricle. This functioned properly for several months, but then she complained of twitching of her right side when she turned on that side while lying in bed. Electrocardiogram revealed that the pacemaker was no longer stimulating the ventricles. Chest Xray is shown in Figure 2. What has happened to the catheter, what caused the twitching and why?



Fig. 2—Case 1—Chest Xray.

The Xray shows recoil of the catheter electrode into the right atrium with twisting of the lead wires near the pulse generator. This is an example of the Pacemaker Twiddler's Syndrome.[1] Some patients develop the habit of twisting the pacemaker in its pocket, winding up the wires, displacing the catheter, and occasionally breaking the wires. This can be prevented by anchoring the pulse generator in its pocket.

The twitching observed by the patient was

*Clinical Assistant Professor, Department of Medicine, University of Minnesota.

Cases presented at ECG Conference, Mt. Sinai Hospital, Minneapolis.

caused by intermittent stimulation of the right phrenic nerve. When the patient rolled to the right, the tip of the catheter, floating in the right atrium, would migrate by gravity to the lateral wall in close proximity to the right phrenic nerve. Right diaphragmatic contraction was a clue to the displacement of the catheter tip into the right atrium.

Case 2

A 68-year-old man was admitted to the hospital because of fainting. Telemetric ECG monitoring demonstrated intermittent complete A-V block with periods of asystole as long as three seconds. A temporary intravenous catheter pacemaker was inserted into the heart with apparent satisfactory position of the electrodes as shown on the PA chest film (Figure 3). The electrocardiogram taken during pacing is shown in Figure 4.

Although the catheter appeared to be in satisfactory position at the apex of the right ventricle, the lateral view of the chest (Figure 5) showed the pacemaker curving posteriorly into the coronary sinus instead of anteriorly into the right ventricle. Both PA and lateral views were necessary to be sure that the pacemaker was in correct position. The electrocardiogram shows pacing of the atrium via the coronary sinus with inverted P waves in leads 2, 3, and AVF. Since the patient did not have A-V block at the time the ECG was recorded, there is normal A-V conduction of the atrial-paced beats.



Fig. 3—Case 2—Chest Xray.

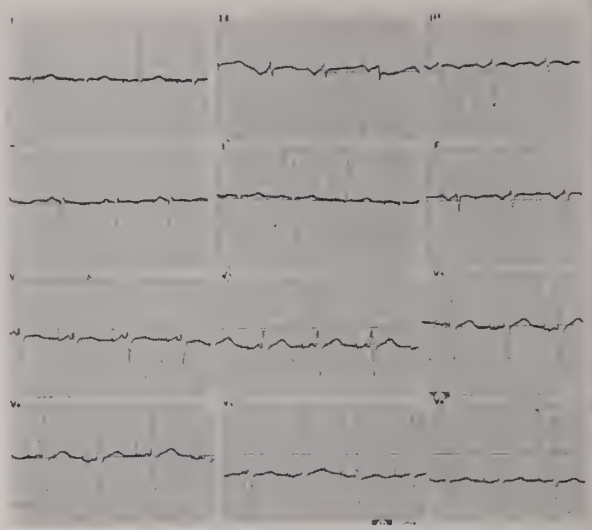


Fig. 4—Case 2—ECG.

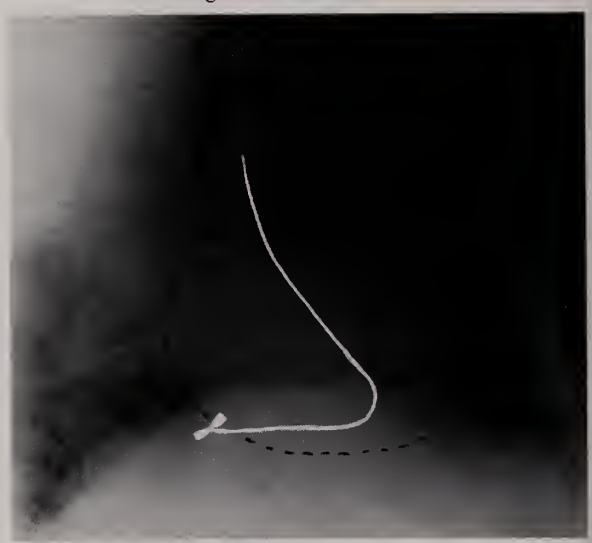


Fig. 5—Case 2—Lateral view of chest. Pacemaker in coronary sinus. (retouched for clarity)

Coronary sinus pacing is an acceptable method of pacing in the absence of A-V block, as in the sick sinus syndrome, and has the advantage of preserving normal atrial-ventricular contraction sequence.[2] In the presence of A-V block, coronary sinus pacing would not be effective. The temporary catheter was replaced with a permanent demand-type pacemaker with the electrode in the right ventricle. The patient had no further difficulty.

Direct ventricular pacing is also possible with coronary sinus pacing. The coronary sinus runs posteriorly in the A-V groove, and, depending on the direction of the catheter tip, the pacing stimulus can be delivered either to the atrium or ventricle. Figure 6 shows intermittent stimulation of the atrium and the left ventricle with a coronary

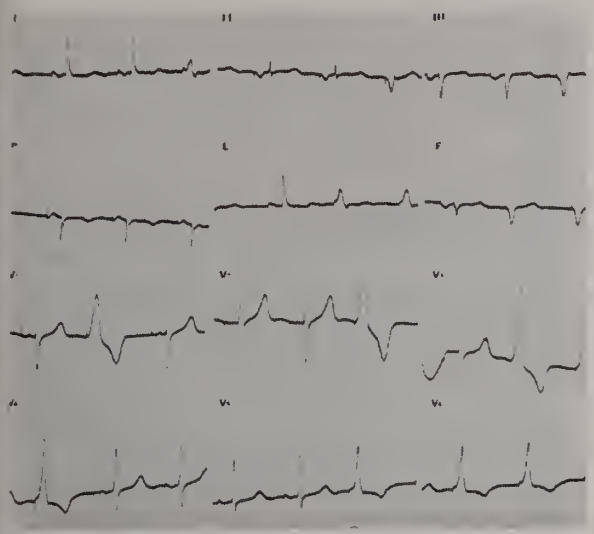


Fig. 6—ECG showing pacing of atrium alternating with direct stimulation of left ventricle.

sinus pacemaker. Left ventricular paced beats have a right bundle branch block configuration (upright QRS complexes in V 1 and 2) as opposed to the more usual left bundle branch block type of QRS complexes seen with right ventricular pacing.

Case 3

A 68-year-old woman had episodes of slow A-V junctional rhythm (sick sinus syndrome). A permanent demand pacemaker with flange tip catheter was inserted into the right ventricle. The following day she complained of intermittent twitching of the left chest. Left diaphragmatic contractions were apparent and the patient was returned to the x-ray department for repositioning of the catheter. Shortly after manipulating the catheter, the patient complained of severe chest pain and had a sudden drop in blood pressure with distension of neck veins.

Left diaphragmatic stimulation in this patient suggested perforation of the right ventricle with the electrode lying in the pericardial space stimulating the left phrenic nerve. Withdrawing the catheter into the ventricle led to hemopericardium and tamponade. Immediate thoracotomy was performed and 600 cc. of blood removed from the pericardial sac. Blood pressure promptly returned to normal. Epicardial pacemaker leads were then inserted, and the patient subsequently did well.

Catheter perforation of the right ventricle is rare, and is usually not accompanied by tamponade.[3] Left diaphragmatic contractions were the initial clue, but can also occur without perforation.[4] Prompt recognition and treatment of tamponade prevented a disastrous outcome. A pericardial friction rub may also be the clue to perforation.

Case 4

A loud presystolic sound was heard intermittently along the left sternal border synchronous with the pacemaker artifact (Figure 7). It was not audible with the normally conducted beats.

The sound was due to contraction of intercostal skeletal muscle associated with position of the electrodes close to the chest wall.[5] Often the muscle twitch is visible and palpable and may be perceived by the patient. Rarely it is associated with perforation of the ventricle. Usually it is a benign finding and the patient should be reassured. Other auscultatory findings associated with pacemakers include: Variation in the intensity of the first heart sound, atrial sounds, and squeaky or scratchy midsystolic murmurs heard at the lower left sternal border.[6] The latter are presumably due to minimal tricuspid insufficiency associated with the catheter passing across the valve.

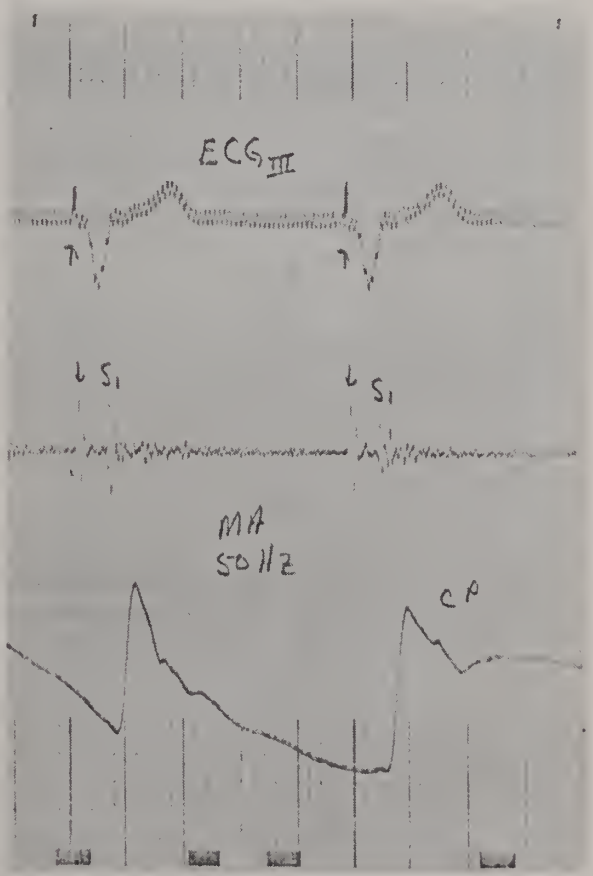


Fig. 7—Case 4—Phonocardiogram. Presystolic pacemaker sound indicated by arrows.

Case 5

This is a rhythm strip from a patient with a demand-type pacemaker inserted because of sick sinus syndrome, slow A-V junctional rhythm, and episodes of atrial fibrillation (Figure 8).

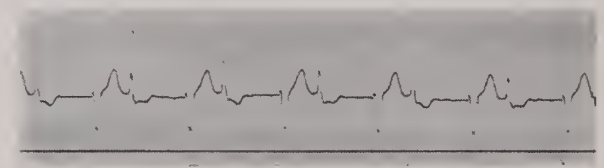


Fig. 8—Case 5—Rhythm Strip. Pacemaker bigeminy.

The basic rhythm was atrial fibrillation with complete A-V block and a slow A-V junctional rhythm. The demand pacemaker fires after a pause, but because of block to retrograde conduction does not depolarize the A-V junctional pacemaker. This then initiates another normally conducted beat accounting for the bigeminal rhythm. This represents proper function of the demand pacemaker and should not be interpreted as a malfunction.

Case 6

This patient had a Devices(T) pacemaker implanted with a unipolar electrode inserted into the right ventricle because of sick sinus syndrome. The rhythm strip (Figure 9) was obtained while a magnet was applied to the pulse generator. The rhythm strip shows failure of the pacemaker to stimulate the ventricles. The magnet converts the Devices(T) pacemaker to a fixed rate of 110. The pacemaker artifacts appear somewhat similar to the QRS complexes, but they are not followed by T waves nor did they produce ventricular contractions. The catheter was repositioned in the right ventricle and satisfactory pacing was again achieved.

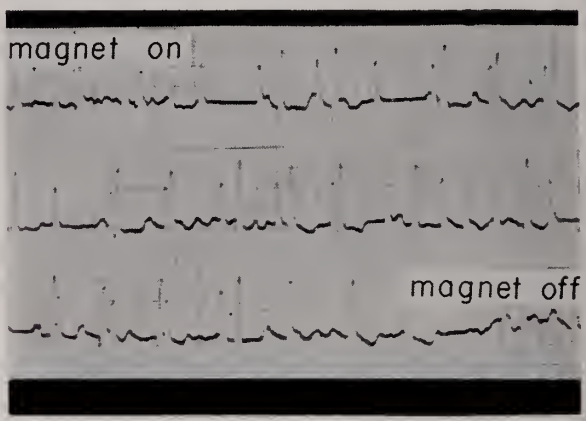


Fig. 9—Case 6—Rhythm Strip.

These are examples of some of the problems encountered in patients with artificial pacemakers. As more of these devices are inserted, an increase in such complications is to be expected.

On the other hand, some problems associated with earlier pacemaker models including inhibition of demand pacemakers by external stimuli; such as microwave ovens, and runaway pacemaker caused by rise in rate with battery depletion have been largely corrected with improvements in design.

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Fall Seminar Offered

Saturday, November 8th, 1975, the Subcommittee on Alcohol and Other Chemical Dependencies is presenting a one-day Seminar entitled "Handling Chemical Dependency problems in the office practice." There will be several short lectures dealing with prevention, early intervention, treatability and referral of clients you suspect to have drug related problems. All Physicians and spouses are invited to attend. The Seminar will be held at the Radisson South, 7800 Normandale Blvd. Registration is $15.00 for Physician and $5.00 for the spouse to include luncheon. An added attraction for those interested, is November 9th, the Minnesota Vikings meet Atlanta in the Met Stadium at 1:00 p.m. All hotel arrangements must be made directly with the hotel. To call the Radisson South, dial (612) 835-7800.

Blastomycosis of the Cervical Spine

LEONARD A. TITRUD, M.D.*

The case illustrates the difficulty of diagnosing blastomycosis. At first the bone destructive lesion was suspected to be a tumor but was later identified as blastomycosis presumably secondary to a pulmonary infection. Supportive surgery and then specific antibiotic treatment resulted in a favorable response to an otherwise dangerous situation.

INFECTIONS WITH THE FUNGUS, blastomycosis occur in North and South America, Mexico and Africa.[1] In the United States it is most prevalent in the Mississippi and Ohio Valleys and in the mid-Atlantic States.[2,3] Agricultural workers are most frequently infected. The port of entry is usually through the respiratory tract with pulmonary involvement such as with other fungus diseases, although direct skin infection may occur. The systemic spread is hematogenous affecting the lungs, bones, and skin most commonly,[4-7] and other tissues as the reticuloendothelial, subcutaneous, meningeal and prostate less often.[8,9] The central nervous system is rarely involved.[8] Fever, coughing, sputum raising, chest pain, malaise, and weight loss herald the disease. Pneumonia is usually suspected and the response to antibiotics is not dramatic.

The nature of the tissue reaction is that of a diffuse, necrotic, granulomatous suppuration. The infecting organism is a spore five to 15 microns in diameter with a thick double contoured and refractive cell wall. They are round or oval and unicellular having a cytoplasm containing refractive granules and vacuoles.[8] The South American type is much larger. Reproduction is by budding. The mycelial form is not seen. Epithelioid, giant, and pus cells are distributed throughout the lesion. The fungus is also distributed through the diseased tissue and stains poorly. Hematoxylin and eosin or periodic Shiff stains will demonstrate the organism.

Intradermal skin tests and determination of positive complement titers are used for suspected cases. Complement—fixing antibodies are usually demonstrated in the sera of patients with generalized blastomycosis.[9] Most patients are hypersensitive to the fungus or fungus products as shown by skin tests with vaccines or extracts of the organism. The more definite diagnosis is provided by culturing infected tissue on Sabouraud's glucose agar medium or on brain—heart infusion agar and then studying the appropriately stained material microscopically. Treatment is directed toward debridement of accessible infected areas and the intravenous administration of gradually increasing doses of amphotericin B or 2-hydroxystilbamidine over a long period of time.[10] Renal toxicity will regulate the intensity of this chemotherapy. The ultimate results of improvement and control of the infection with such treatment has been fairly good.[6]

Case Report

A 38-year-old white male native of Minnesota with good previous health developed pneumonia in April 1971 with a temperature of 100°F. and a leukocyte count of 12,600 per cu mm. The chest Xray revealed a lateral right hilar infiltrate. He became well over a three week period while receiving Bicillin and Achromycin. In the spring of 1972, discomfort developed within his throat and neck. A retropharyngeal lesion was suspected. In June 1972 cervical spine Xrays showed bone destruction involving the second and third cervical vertebral bodies. A transoral biopsy obtained tissue which was believed to show an eosinophilic granuloma. The patient was then fitted with a neck brace and returned to work in a lumber yard. Suboccipital pain, anorexia and weight loss developed by October 1972.

Hospitalization was required again in December 1972.

*Minneapolis, Minnesota.

Spinal fluid examination showed one leukocyte per cu mm and a protein content of 55 mg per 100 ml. The first cervical vertebra was biopsied transnasally January 7, 1973 and the tissue obtained showed inflammatory changes. The erythrocyte sedimentation rate varied from 54 to 86 mm per hour measured over a number of days. On February 7, 1973, a large right cervical lymph node was removed and this tissue was considered to be normal. Because an infectious process was suspected in addition to eosinophilic granuloma, the patient received both antibiotic treatment as well as x-ray therapy that was administered in eight treatments from January 10 to 19, 1973 with a total dose of 1600 rads. Additional Xrays revealed a collapse of the first and second cervical vertebrae and some destruction of the third also. Planograms made suggested that there was a polypoid soft tissue mass in the posterior nasopharynx.

He continued to have neck pain and a Peterson brace was fitted. The brace proved uncomfortable, and he would often take it off and sit supporting his head with one hand. He tended to flex his head and have it rotated to the right in order to reduce arm pain which had developed by this time. Neurological examination seemed to be normal. He received analgesic and sedative medications and also cervical traction with a halter that provided some comfort. Because of fear that his spinal cord might become compressed, a posterior cervical fusion was done on March 19, 1973. The second cervical lamina and spinous process were found to be loose and the bone of the lamina and lateral process on the left side were destroyed. There was a cheesy and friable light tan colored tissue extradurally which was removed for laboratory examination. After this debridement two low occipital bone drill holes were made and two double strands of #20 stainless steel wires were placed under the remaining laminae of the first, second, and third cervical vertebrae and through the occipital bone holes and tightened securely. Strips of bone were obtained from the posterior iliac crest and applied over the denuded bone surface from the occiput to the third cervical vertebra. After the wound was sutured and dressed, the posterior half of a Minerva cast was applied over and about the head, neck and trunk. On March 21, 1973 the anterior part of the Minerva cast was applied incorporating the posterior half. He tolerated these procedures well.

Microscopic examination of the necrotic tissue from the depths of the operative wound revealed large areas of granulomatous inflammatory reaction characterized by neutrophiles, histiocytes, epithelioid cells and large irregular areas of necrosis (Figure 1). PAS and silver stains showed the presence of several thick walled budding yeast forms within this inflammatory material. Mucicarmine stains had a negative reaction. These single budding yeast forms had the morphological features of North American blastomycosis (Figures 2 and 3). Unfortunately the material sent to the laboratory for cultures was lost.

This patient was transferred from the private hospital to the Minneapolis Veterans Administration Hospital March 23 and remained there until September 6, 1973, receiving treatment with amphotericin B and rehabilitation. His neurological examination was normal at the beginning of this period except for slight increase of the radial, biceps, and triceps reflexes, and some right ankle clonus. Intravenous amphotericin B treatment was commenced on March 30 and continued until July 13, 1973, a total dose of 2200 mgms being given. The Minerva cast was replaced with a body cast having a Halo cranial fixation attachment on May 3 and was worn until August 31 when he was fitted with a Peterson brace. During this time he gained weight and began to feel stronger in general.

Cervical spine Xrays, including planograms, made June 2, July 2, and July 5, 1973 showed the anterior arch of the first cervical vertebra and the odontoid

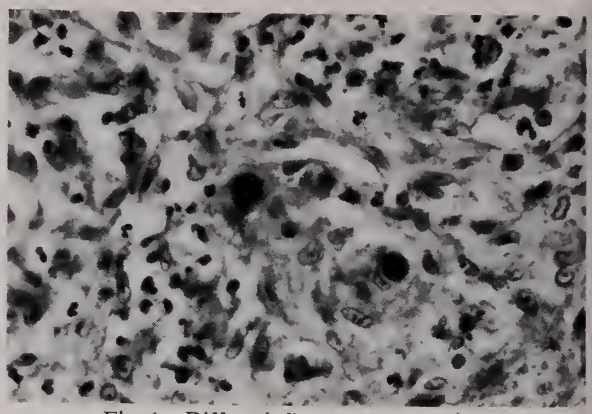


Fig. 1—Diffuse inflammatory reaction.

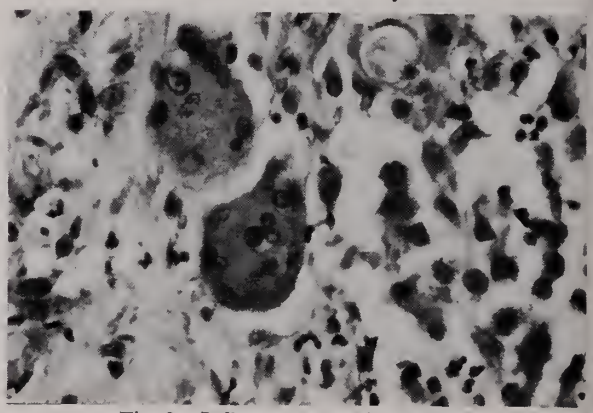


Fig. 2—Inflammatory cell response.

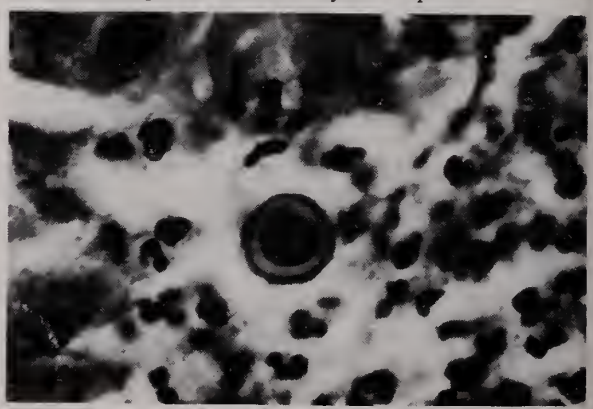


Fig. 3—Blastomycosis spore.

process to be absent. The left side of the third cervical vertebra had a diminished height and the second cervical vertebra had a forward subluxation on the third. There was irregularity in the contour of the second and third cervical vertebrae with some destruction of the interspace between them. The bone density seemed increased. Cervical spine Xrays of August 23 and December 6, 1973 demonstrated posterior bone fusion occurring. Partial destruction of the third cervical vertebra anteriorly together with some of the second and the odontoid process was also seen. The anterior and lateral parts of the first cervical vertebral arch were destroyed also (Figures 4, 5 and 6).

The patient was reexamined on February 7, 1974. He had returned to work as a lumber yard manager and was feeling well. Cervical spine Xrays at this time demonstrated bone fusion to be continuing well. He was still feeling well and was working full time when last seen in November 1974.

Conclusion

The diagnosis of this infrequent disease is often difficult. Usually it simulates the other mycotic infections. Whereas, blastomycosis, candidemia, coccidiodomycosis, sporotrichosis, cryptococcosis, and histoplasmosis have a favorable response to amphotericin B; tuberculosis, actinomycosis and nocardiosis respond better to other antibiotics.[11] Hydroxystilbamidine is considered less toxic than amphotericin B and should be the first one ad-



Fig. 5—Destruction in I, II, III cervical vertebrae.



Fig. 4—Destruction in I, II, III cervical vertebrae.



Fig. 6—Destruction in I, II, III cervical vertebrae.

ministered for North American blastomycosis reserving amphotericin B for those severely ill with systemic disease.[11,12] Obviously, the diagnosis and specific chemotherapy are of the first importance, and any surgical treatment that may be needed will depend upon the individual patient's illness.

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STATE OF MINNESOTA
COUNTY OF RAMSEY

BEFORE THE STATE BOARD
OF MEDICAL EXAMINERS

NOTICE OF HEARING

In the Matter of the Proposed Adoption of Amendments to Rules ME 1(c), ME 2(b) (3), ME 2(b) (4), ME 2(b) (5), ME 2(b) (6), ME 2(b) (7), ME 2(c), ME 3(a), ME 3(b), ME 3(c), ME 3(d), ME 4(b) (5), ME 5(a), ME 5(b) (1), ME 6(b) (8), ME 7(a) (1), ME 7(a) (7), ME 7(a) (8), ME 8(b) (3), ME 8(c), ME 10 and ME 31-41 of State Board of Medical Examiners

Notice is hereby given that a public hearing will be held pursuant to Minnesota Statutes 1974, Section 15.0412, Subd. 4, in the above-entitled matter in Suite 203, Minnesota State Bank Building, 200 South Robert Street, St. Paul, Minnesota 55107, on Saturday, November 15, 1975, commencing at 11:00 o'clock a.m. and continuing until all representatives of associations or other interested groups or persons have had an opportunity to be heard concerning adoption of the proposed amendments to rules captioned above by submitting either oral or written data, statements or arguments. Statements or briefs may be submitted without appearing at the hearing.

Under Minnesota Statutes 1974, Section 10A-01, Subd. 11, any individual representing persons or associations attempting to influence administrative action, such as promulgation of these amendments to rules, must register with the State Ethics Commission as a lobbyist within five days of the commencement of such activity by the individual. The State Ethics Commission is located at 410 State Office Building, St. Paul, Minnesota 55155.

Copies of the proposed amendments to rules are now available and may be obtained by writing to Arthur W. Poore, Executive Secretary, State Board of Medical Examiners, Suite 203, Minnesota State Bank Building, 200 South Robert Street, St. Paul, Minnesota 55107.

STATE BOARD OF MEDICAL EXAMINERS
Bror F. Pearson, Secretary-Treasurer

Carcinoma of the Cervix

Clinical and Surgical Staging

ROBERT D. HILGERS, M.D.*

The International Classification used to stage patients with carcinoma of the cervix is reviewed. The error in staging disease by physical examination arises from metastatic spread to inaccessible anatomical areas. As a consequence, alternative methods are being investigated in an attempt to improve the accuracy of clinical staging.

THE MANAGEMENT OF PATIENTS with carcinoma of the cervix depends upon an accurate estimate of the extent of disease present at the time of treatment. Since 1920,[1] several attempts have been made to correlate the pattern of natural growth with the clinical extent of disease. In 1929, the original League of Nations Classification[2] conceptualized this correlation into four stages of cervical carcinoma with ascending stages corresponding to greater degrees of tumor involvement. Staging, thus defined, was derived from the clinical examination. Understandably, this classification has been revised on several occasions to meet the needs of new information.

Staging patients prior to treatment is especially important as it represents a standard uniform system which gives the physician a reference point for determining adequate and meaningful treatment as well as for comparing his results with others. Unfortunately, clinical staging is limited to evaluating the pelvic structures and to detecting distant metastases. It does not take into account interval metastases, i.e. in the retroperitoneal para-aortic lymph nodes or in the peritoneal cavity, which usually lie outside the area covered by conventional treatment fields.

Clinical Staging

The International Classification recommended for staging patients with carcinoma of the cervix is outlined in Table 1.[3,4]

A few general rules apply to staging patients with cervical carcinoma. Notably important, staging is based on findings derived from the clinical examination. The clinical examination may be performed on either the awake or the anesthetized patient. The stage of the disease must be determined before therapy is begun; once the classification has been established and treatment begun, the classification cannot be changed. The neoplasm obviously must arise from the cervix and each of the histological types are included. Patients with

TABLE 1
FIGO Staging System

STAGE 0:	Carcinoma in situ
STAGE I:	Carcinoma strictly confined to cervix.
Ia:	Cannot be diagnosed by clinical examination (1) Early Stromal Invasion (2) Occult Carcinoma
Ib:	All other cases of Stage I.
STAGE II:	Carcinoma extends beyond cervix but not on to pelvic wall. Involves upper two-thirds of vagina.
IIa:	No parametrial involvement.
IIb:	Obvious parametrial involvement.
STAGE III:	Carcinoma extends on to pelvic side wall. Involves lowest third of vagina.
IIIa:	No extension on to pelvic side wall.
IIIb:	Extension on to pelvic side wall.
STAGE IV:	Extends beyond true pelvis or has involved the mucosa of the bladder or rectum.

Approved January 1, 1971.

*American Cancer Society Junior Faculty Fellow and Associate Professor of Obstetrics and Gynecology, Division of Gynecological Oncology, University of Minnesota School of Medicine, Minneapolis, Minnesota.

Reprint requests: Robert D. Hilgers, M.D., Box 395, Mayo Memorial Building, University of Minnesota Hospitals, Minneapolis, Minnesota 55455.

See editorial, page 743.

recurrent disease are not included in this staging system.

Clinical staging is based on palpation, inspection, chest Xray, skeletal survey and intravenous pyelography (Table 2). Methods of inspection (Table 3) include cystoscopy and proctoscopy, examinations required in staging every patient. Colposcopy and hysteroscopy are permitted but are usually not necessary. Conization of the cervix is regarded as a clinical examination and an invasive carcinoma established by this method should be reported as invasive carcinoma. Abnormal cytology is not essential for staging; it indicates that a cervical biopsy should be performed. Conversely, the procedures listed in Table 4 are not appropriate for staging purposes. These are special diagnostic methods which are either not available to every physician or are controversial in their interpretation.

TABLE 2
Diagnostic Methods Approved for Clinical Staging

Palpation
Inspection
Chest Xray
Skeletal Survey
IVP

TABLE 3
Methods of Inspection

Colposcopy
Conization
Cystoscopy
Fractional Curettage
Hysteroscopy
Sigmoidoscopy

TABLE 4
Diagnostic Methods Not Approved For Clinical Staging

Angiography
Hysterography
Laparoscopy
Laparotomy
Lymphangiography
Venography

Stage 0 or carcinoma in situ is not considered a reportable disease and therefore should not be included in any therapeutic statistics.

Patients with preclinical invasive carcinoma are classified *Stage Ia*. This group includes cases with early stromal invasion or occult carcinoma. Early stromal invasion represents the very earliest and most minimal break-through of the basement membrane. Occult carcinoma is a fully developed invasive lesion with microscopically detected islands of malignant cells well out in the stroma. Cases of microscopically invasive carcinoma unexpectedly diagnosed on a routine hysterectomy specimen should be classified "Stage Ia-post-surgical."

Tumor extending into the uterine corpus should be disregarded in patients with *Stage I* disease.

The presence of hydronephrosis or a non-functioning kidney, due to stenosis of the ureter by tumor, permits allotment of the case to *Stage III* even if according to the other findings the case should be allotted to an earlier stage.

Biopsy proven invasion of the bladder mucosa represents *Stage IV* disease. Bullous edema without mucosal invasion does not change the original clinical staging. Ridges and furrows into the bladder wall, if fixed to the primary growth, should be interpreted as evidence of submucosal involvement of the bladder.

Like all clinical staging procedures, staging carcinoma of the cervix has its limitations. As an example, no extension can be palpated beyond the cervix in Stage I disease; yet 16.5% of patients have metastases in their pelvic lymph nodes.[5] Similarily, the size of the lesion and subclinical or microscopic parametrial involvement are not included in the classification. In Stage II, where tumor invades intermediate pelvic tissues, pelvic lymph node metastases are present in 31.9% of patients.[5] Failure to palpate tumor in the parametria or to properly interpret parametrial induration is a common error in patients with either Stage I or II disease. It is difficult to clinically diagnose the true status of the parametria, as an indurated parametrium is not necessarily cancerous and a palpably free parametrium does not exclude cancer. Nor does a microscopically free parametrium obviate the presence of regional or distant nodes. Furthermore, in over one-third of the patients with Stage III disease tumor cells are present in the para-aortic lymph nodes. These metastases are especially difficult to diagnose unless surgical staging has been performed or a clearly positive lymphangiogram has been obtained. Errors in diagnosing Stage IV disease are seldom made as the extent of disease is usually self evident.

Because the pelvic structures are relatively inaccessible to examination, clinical staging remains a relatively inaccurate method for determining

tumor spread. This is true whether the patient is examined awake or under anesthesia. Greater pelvic relaxation can be obtained however by examining the patient under anesthesia. When laparotomy findings are compared with clinical staging, the clinical staging will be in error in about 50% of patients staged without anesthesia and 25% of patients staged with anesthesia.[6]

Surgical Staging

Because of the above limitations in clinical staging other methods of determining tumor spread are currently under investigation.

Surgical staging or staging at laparotomy is one means of improving the accuracy of staging patients with carcinoma of the cervix. The distribution of tumor is documented by exploring the pelvic and para-aortic spaces and by sampling lymph nodes from the various lymphatic chains. The presence of liver, omental and/or bowel metastases are noted. Finally, the findings determined by clinical and surgical staging are compared using the Meigs-Brunschwig Surgical Pathologic Classification.[7] Results from two series are outlined in Table 5.[8,9]

It is important to emphasize that *surgical staging remains an investigative tool and it is not recommended for the routine care of cervical carcinoma patients.*

There are reasons for defining its role before recommending it as a standardized procedure; the obvious one relates to the morbidity of the procedure. If the morbidity is greater than the benefit gained, then the procedure will not serve a useful purpose. The ultimate goal is to improve overall survival; alternative treatment plans resulting from such a procedure will necessarily have to manifest survival figures which are superior to those now obtained by conventional therapy.

TABLE 5
Clinical Staging Versus Surgical Staging

Clinical Stage	Percent Error Van Nagell (1971)	Averette (1972)
IB	(67) 22%	(40) 20%
IIA	(33) 45%	(9) 44%
IIB		(9) 56%
III	(16) 75%	(10) 100%
IV	(9) 0%	(2) 0%
Overall Error	(125) 44%	(70) 39%

( ) Total number of patients studied.

Preliminary information gleaned from patients staged by laparotomy indicates that a direct relationship exists between the incidence of para-aortic lymph node metastases and the clinical stage of disease. Table 6 shows that the frequency of occurrence increases as the clinical stage advances. Liver, bowel and omental metastases have also been observed in patients with proven para-aortic node metastases (Table 7).

Traditionally, patients with para-aortic lymph node involvement have been considered incurable. It previously represented disease which had spread

TABLE 6
Frequency of Para-Aortic Node Metastases

Source	Clinical Stage I	II	III	IV
Averette, 1972	(40) 7.5%	(18) 22 %	(10) 20%	(2) 50%
Buchsbaum, 1974	———	(12) 8 %	(37) 35%	(3) 66%
Nelson, 1974	———	(31) 16 %	(28) 46%	———
Piver, 1974	———	(19) 5.2%	(32) 38%	(5) 40%

( ) Total number of patients studied.

TABLE 7
Metastases In Patients With Proven Para-Aortic Node Involvement

Source	No. of Patients	Metastatic Sites
Buchsbaum, 1974	4/15	2-liver 2-bowel
Nelson, 1974	0/18	1-bowel
Piver, 1974	3/15	2-liver 1-omentum

beyond the pelvis where eurative doses could not be administered to the tissue volumes involved.

These conventionally held coneepts are now being ehallenged by extending the field as well as inereasing the dose of irradiation to microscopically proven para-aortic node metastases.[15] Although few reports contain an adequate number of patients followed five years, a small percentage of patients have been eured by this approaeh (Table 8).

TABLE 8
Effect of Radiating Para-Aortic Nodes

Source	Dose Level	Survival Pattern
Silberstein, 1970	6000r/6wks	3 of 6 pts. (3-11 years)
Averette, 1972	4000r	Not stated
Fletcher, 1972	5000r/6wks	10 of 41 pts. (18 mo.-10 years)
Buchsbaum, 1974	5400r/6wks	5 of 10 pts. (5-30 months)
Nelson, 1974	6000r/6wks	Not stated
Piver, 1974	6000r/8wks	30% at 24 mos.

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Cover Photograph

"The Birches of Bay Lake"

Dr. Richard Waehter took the cover photograph in Oetober, 1974, on one of those beautiful Indian summer days, late in the afternoon. Bay Lake is twenty miles east of Brainerd, Minnesota, and has many stands of these beautiful birch trees.

Dr. Waehter finished a neuro-radiology fellowship at the University of Minnesota Hospitals in July of this year and is presently in the U.S. Navy at Jacksonville, Florida.

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Precautions: Addiction (dependency) to diphenoxylate HCl is theoretically possible at high dosage. Do not exceed recommended dosages. Administer with caution to patients receiving addicting drugs or known to be addiction prone or having a history of drug abuse. The subtherapeutic amount of atropine is added to discourage deliberate overdosage; strictly observe contraindications, warnings and precautions for atropine; use with caution in children since signs of atropinism may occur even with the recommended dosage. Use with care in patients with acute ulcerative colitis and discontinue use if abdominal distention or other symptoms develop.

Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing, hyperthermia, tachycardia and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria, paralytic ileus, and toxic megacolon.

Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

Overdosage: Keep the medication out of the reach of children since accidental overdosage may cause severe, even fatal, respiratory depression. Signs of overdosage include flushing, hyperthermia, tachycardia, lethargy or coma, hypotonic reflexes, nystagmus, pinpoint pupils and respiratory depression which may occur 12 to 30 hours after overdose. Evacuate stomach by lavage, establish a patent airway and, when necessary, assist respiration mechanically. A narcotic antagonist may be used in severe respiratory depression. Observation should extend over at least 48 hours.

Dosage forms: Tablets, 2.5 mg. of diphenoxylate HCl with 0.025 mg. of atropine sulfate. Liquid, 2.5 mg. of diphenoxylate HCl and 0.025 mg. of atropine sulfate per 5 ml. A plastic dropper calibrated in increments of ½ ml. (total capacity, 2 ml.) accompanies each 2-oz. bottle of Lomotil liquid.

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Each tablet and each 5 ml. of liquid contain: diphenoxylate hydrochloride 2.5 mg. (Warning: May be habit forming), atropine sulfate 0.025 mg.

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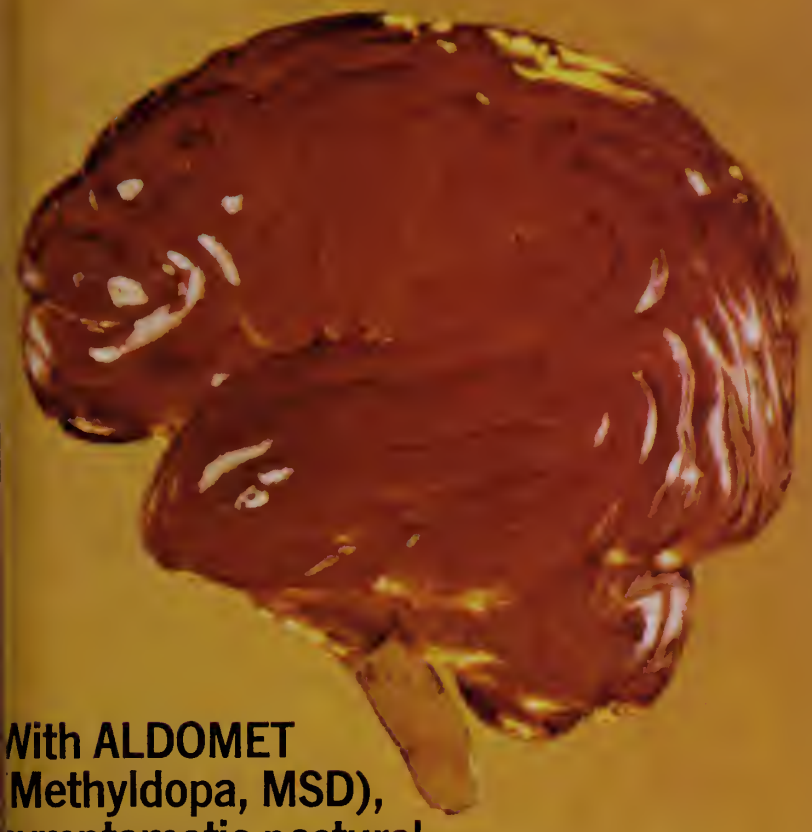


With ALDOMET (Methyldopa, MSD), existing renal function is usually unchanged

ALDOMET has no direct effect on renal function. When used in effective doses, ALDOMET usually does not reduce glomerular filtration rate, renal blood flow, or filtration fraction.

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ALDOMET has no direct effect on cardiac function. When ALDOMET is used in effective doses cardiac output is usually maintained with no cardiac acceleration; in some patients the heart rate is slowed.



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ALDOMET reduces both supine and standing blood pressure. Less frequent symptomatic postural hypotension is experienced with ALDOMET than with many other antihypertensive agents. Exercise hypotension and diurnal blood pressure variations rarely occur.

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TABLETS, 250 mg, 500 mg, and 125 mg

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ALDOMET is contraindicated in active hepatic disease, hypersensitivity to the drug, and if previous methyldopa therapy has been associated with liver disorders. It is not recommended in pheochromocytoma.

It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. For more details see the brief summary of prescribing information.

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For a brief summary of prescribing information, please see following page.

addendum

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to further simplify therapy for many patients

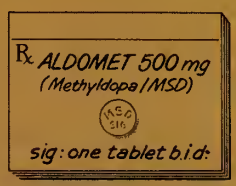
now available ALDOMET® 500 mg (METHYLDOPA|MSD)

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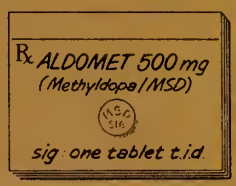
Now offered in addition to the standard 250-mg tablet, the new ALDOMET 500 mg tablet is a patient convenience. An especially important one, since in hypertension convenience of the dosage schedule is one factor that can make the difference in compliance of the patient. The minimum daily dose of ALDOMET is 250 mg b.i.d. The usual starting dose is 250 mg t.i.d. Dosage is adjusted as necessary by adding or deleting 250 mg or 500 mg at intervals of not less than two days. The maximum dose is 3.0 g per day.

Examples of b.i.d. or t.i.d. dosage convenience provided by ALDOMET 500 mg within the usual daily dosage range of 500 mg to 2.0 g:

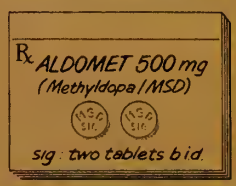
1.0-g daily dose =

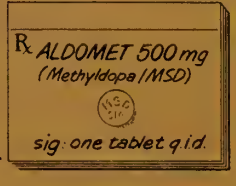


1.5-g daily dose =



2.0-g daily dose =





NOTE: Tablets shown are not actual size.

in hypertension

ALDOMET® (METHYLDOPA|MSD)

usually lowers blood pressure effectively



Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reaction or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites

Stop drug if involuntary choreoathetotic moven occur in patients with severe bilateral cerebrov lar disease. Patients may require reduced dos anesthetics; hypotension occurring during thesia usually can be controlled with vasopres Hypertension has recurred after dialysis in pat on methyldopa because the drug is removed b procedure.

Adverse Reactions: *Central nervous sys* Sedation, headache, asthenia or weakness, u early and transient; dizziness, lightheaded symptoms of cerebrovascular insuffici paresthesias, parkinsonism, Bell's palsy, involu choreoathetotic movements; psychic disturba including nightmares and reversible mild psycl or depression.

Cardiovascular: Bradycardia, aggravation of a pectoris. Orthostatic hypotension (decrease dosage). Edema (and weight gain) usually re by use of a diuretic. (Discontinue methyldo edema progresses or signs of heart failure ap

Gastrointestinal: Nausea, vomiting, diste constipation, flatus, diarrhea, mild drynes mouth, sore or "black" tongue, pancre sialadenitis.

Hepatic: Abnormal liver function tests, jau liver disorders.

Hematologic: Positive Coombs test, hem anemia. Leukopenia, granulocytopenia, th bocytopenia

Allergic: Drug-related fever, skin rash.

Other: Nasal stuffiness, rise in BUN, breast en ment, gynecomastia, lactation, impot decreased libido, mild arthralgia, myalgia.

Note: Initial adult dosage should be limit 500 mg daily when given with antihyperte other than thiazides. Tolerance may occur, u between second and third month of therap creased dosage or adding a thiazide freq restores effective control. Patients with im renal function may respond to smaller doses cope in older patients may be related to inc sensitivity and advanced arteriosclerotic va disease; this may be avoided by lower doses

How Supplied: Tablets, containing 1 methyldopa each, in bottles of 100; Tablets, c ing 250 mg methyldopa each, in singl packages of 100 and bottles of 100 and Tablets, containing 500 mg methyldopa ea single-unit packages of 100 and bottles of 1

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Editorials

Carcinoma of the Cervix

Clinical and Surgical Staging

DR. HILGERS* PRESENTS a brief discussion of the history of the development of the International Classification of Carcinoma of the Cervix, accentuates the deficiencies of clinical staging, and discusses potential advantages of surgical staging as delineated by some of the current relevant literature.

The inaccuracy of clinical staging has been well documented. Claiborne et al.[1] in 1960 collected cases from eight authors and reported incidences of regional lymph nodes metastases in 16.6 percent of 857 Stage I patients and in 32.2 percent of 832 patients with Stage II carcinoma of the cervix. Similar findings were reported by Navratil Graz[2] in 1955 with a review of 1,643 cases showing lymph nodes metastases in Stages I and II of 17.2 and 32.9 percent respectfully. Errors in Stage III vary from 30 percent to 100 percent as recently reported following surgical staging by Averette et al.[3]

Staging serves two important functions. First to indicate a protocol of therapy based on the extent of disease and second, following the program of therapy to effectively evaluate the efficiency of that therapy.

At this time there appears a need to evaluate other methods of staging carcinoma of the cervix. As Dr. Hilgers points out in his article evaluation must include the morbidity and mortality of additional staging procedures, e.g. exploratory celiotomy. Assuming surgical staging improves the accuracy of staging whether the resultant extra pelvic radiation will result in an improved cure rate at this time is an unknown and unproved factor.

Certainly at this time, surgical staging of all patients with carcinoma of the cervix does not appear appropriate.

Piver and Barlow[4] recommend utilization of aortic lymphangiography in patients with substantial risk of extra pelvic metastases to indicate which patients should be treated by extra pelvic radiation and which patients should be subjected to exploratory celiotomy. In their series only two of twenty patients with negative lymphangiograms were positive nodes detected by surgical exploration. In 23 of 24 patients with positive lymphangiograms, there was histologic confirmation at the time of surgical exploration. Based on their small series, they recommend the following protocol for patients with advanced carcinoma (Stages III and IV). Patients with positive lymphangiograms are treated by extended field radiation. If aortic node metastases are not demonstrated by para-aortic lymphangiography, then patients with Stages III and IV should undergo explatory celiotomy for evaluation of aortic nodes.

John C. Ellis, Jr., M.D.
Minneapolis, Minnesota

*See page 733.

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Common Sense . . . . . Please!

REHABILITATION PROGRAMS for patients recovering from an acute myocardial infarction are not new. Levine and Lown in 1952 advocated early activity. However, their message was ignored and prolonged strict bed rest was widely accepted until recently. Early mobilization has been rediscovered and is being carried to the extreme. Even before the patient is fully aware of the new drastic situation, great excitement begins, and soon he is engaged in a wrestling match with his physical therapist. Further, he is told in great detail with figures and drawings that he has to start moving according to a rigid, empirical and capricious program.

The patient recovering from an acute myocardial infarct is not an invalid. He is certainly in need of proper coaching and careful advice as far as his activity is concerned. But please . . . no unnecessary acrobatics nor endless list of stages and steps and contortions.

In conclusion, we know that cautious early activity and ambulation is beneficial. But keep in mind that carelessly prescribed exercises can be harmful or lethal. Also let us remember that the easier and simpler the prescription the more likely it is to succeed.

Fouad Azzam, M.D.
Minneapolis, Minnesota

Dextran-40 Anaphylaxis

THE PAPER BY Krenzelok and Parker,* which appeared in MINNESOTA MEDICINE, reporting a rare case of anaphylaxis to Dextran, is appropriate. Although the reported incidence of Dextran-40 anaphylaxis is stated to be one in 300,000, we have seen two occurring with low molecular Dextran and a third occurring with infusion of 6% Gentran-70. The two individuals who received Dextran-40 and developed an anaphylactic reaction both received less than one cc of the drug administered as a test dose in one instance by a nurse and in the other instance by a resident physician. Both of the individuals had no history of any drug allergies. Both required total cardiorespiratory support with external cardiac massage, endotrachael intubation and respiratory assistance and support drug therapy. All of the patients recovered without incidence. The last individual's serum was studied by Dr. P. Maurer, Chairman, Department of Biochemistry at Jefferson Medical College, and after six months the patient's serum still contained significant antigenic effect of Dextran to experimental animals.

In view of the frequent use of Dextran-40 in cardiovascular surgical procedures and as a volume expander in trauma cases, it would seem reasonable that the physician familiarize himself with the potential adverse effect of this drug. Furthermore, it would seem prudent that a test dose be given even in the absence of any history of allergies.

Earl G. Yonehiro, M.D., Ph.D.†
St. Louis Park, Minnesota

*Krenzelok EP and Parker WA: Dextran 40 anaphylaxis. MINNESOTA MEDICINE 58:454, 1975.

†Department of General Surgery, St. Louis Park Medical Center.

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Tetracycline and Acne

THE RECENT ARTICLE by Becker[1] on the effectiveness of tetracycline in the treatment of acne vulgaris is a welcome article. Although not a double-blind study, his data strongly support his previous comments[2] and the common consensus among dermatologists that tetracycline is an effective, and relatively safe antibiotic for use in treating acne vulgaris when systemic antibiotics are required.

The mechanism by which tetracycline exerts its beneficial effects is not completely clear. Most probably its antibiotic property is most important, although it may have additional nonantibiotic pharmacologic effects as well. Microbiologically, three types of microbial organisms are present in the normal sebaceous follicle: (1) *Corynebacterium acnes* (C. acnes) most predominant in the sebaceous follicles, (2) Gram positive cocci most predominant in the follicular mouths, and (3) yeasts *Pityrosporum ovale* and *Pityrosporum orbiculare*.[3,4] While all these organisms may play some role in acne pathogenesis, the anaerobic diptheroid *C. Acnes* is probably most important. This organism splits triglycerides of sebum into free fatty acids *in vivo*.[5] Free fatty acids thus formed may initiate formation of comedones and production of inflammation around sebaceous follicles. C. Acnes is usually sensitive to tetracycline. Thus, the beneficial effect of tetracycline on acne is probably the result of population control of *C. Acnes* with resultant decrease in acne-forming free fatty acids.

Not all patients with acne require systemic antibiotics. On the other hand, control of certain forms of acne, particularly nodulocystic acne, is sometimes impossible without administering systemic antimicrobial agents. Many and perhaps most dermatologists believe tetracycline is the drug of choice for most patients. As Becker points out, it is effective, relatively safe, and inexpensive. At least six double-blind prospective studies have demonstrated effectiveness of tetracycline or its analogues, and most dermatologists are unequivocally convinced of its biologic effectiveness from their own personal experience. The most frequent side effect is probably monilial vaginitis. Anorexia, nausea, vomiting and flatulence are common at high daily dosage levels, but infrequent at dosages commonly employed in acne management. Except in special circumstances, the drug should not be administered to pregnant women since permanent staining of teeth of the fetus may occur. Tetracycline potentiates anticoagulants, and under certain circumstances may perhaps produce liver, renal, or hematotoxicity. A variety of other side effects and hypersensitivity reactions are well documented but also rare.

Although bacterial culture of lesions may show Staphylococcus epidermiditis resistant to tetracycline in treated patients, this is often not clinically relevant since coexisting anaerobic C. Acnes may still be the major pathogen. Indeed, as Becker points out, these patients may obtain adequate remission with higher doses of tetracycline. Much more relevant are infections or superinfections with Klebsiella-enterobacter or proteus gram-negative organisms which may necessitate use of an antibiotic other than tetracycline based on sensitivity tests of the organism involved.[6]

It seems clear from the study of Becker and multiple clinical and laboratory studies of others, that tetracycline is a useful and effective agent for systemic treatment of acne vulgaris. Administration of tetracycline may reduce the severity and frequency of acne comedones, papules, pustules, and cysts and may thus prevent at least some of the permanent and sometimes mutilating scars and keloids which may follow.

Mark V. Dahl, M.D.*
Minneapolis, Minnesota

*Assistant Professor of Dermatology, University of Minnesota Hospitals.

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Streptococcology for the Non-Streptococcologist

"STREPTOCOCCOLOGY FOR the Non-Streptococcologists," published in the August issue* is a delightful and somewhat of a mini-smorgasbord discussion of the streptococci. The literature is replete with research efforts to better understand the streptococci and their relationship to disease, especially rheumatic fever and associated heart disease to which I address this editorial. Many streptococcologists are investigating the possibility of developing a vaccine to protect mankind against the ravages of streptococcal infections, especially rheumatic fever and associated heart disease. To date, success has eluded them. A streptococcal vaccine to prevent rheumatic fever would be the ultimate public health weapon which could lead to the eradication of this disease. Until such vaccine is developed, we have the very current problem of early discovery of persons with acute pharyngitis infected with Group A beta hemolytic streptococci and their treatment with antibiotics or chemotherapeutic agents. The effectiveness of penicillin and sulfa drugs, especially penicillin, in the treatment of beta hemolytic streptococci infections, has led many to believe that early detection of acute streptococcal pharyngitis with prompt treatment would lead to the eradication of rheumatic fever and associated heart disease. An admirable objective to which we all subscribe.

Why hasn't rheumatic fever and associated heart disease been eradicated from Connecticut and Colorado, to name a few states, where aggressive throat culture programs and penicillin prophylaxis have been in operation for a number of years? It is a vexing question for those who promote wholesale throat cultures from persons with acute pharyngitis and treatment, usually with penicillin of those persons showing Group A beta hemolytic streptococci in their culture. Without a vaccine, the most we can hope for is to join the apparent natural declining incidence of rheumatic fever with a carefully designed culture and treatment program based on a defined incidence of rheumatic heart disease.

Since 1960, the Minnesota Department of Health in cooperation with the Minnesota State Medical Association, Minnesota Pharmaceutical Association and Minnesota Heart Association, has operated a "Rheumatic Fever Secondary Prevention Program." Part of this program involves keeping a registry at the Minnesota Department of Health, of reported cases of acute rheumatic fever. In 1960, 3,175 cases were registered and there has been a steady decline through 1972 when 369 cases were reported with a slight increase to 420 cases reported for 1974. Minnesota does not have a state-wide primary prevention program. There is a need to reassess data in our registry, particularly when one considers implementing a primary prevention program which encompasses throat cultures of children with acute pharyngitis and treatment of those with Group A beta hemolytic streptococci in their throat. From September, 1975 through June, 1976, the Minnesota Department of Health will be coordinating a study to help define the incidence of acute rheumatic fever in Minnesota. Individuals under age 20 with onset of acute rheumatic fever in the four months previous to being reported to our rheumatic fever registry will be further evaluated, cooperatively, by the patient's primary physician and one of the pediatric cardiologists participating in the study. Pediatric cardiologists from different areas of the state will assist in the study. This study has been endorsed by the Council, the Heart Committee and the Child Health Committee of the Minnesota State Medical Association. Analysis of the data will be performed next summer; conclusions will be distributed to all physicians. This study should provide us with data to give direction in the development of programs to reduce rheumatic fever and associated heart disease and provide us with a yardstick to measure the success or failure of such programs.

Henry Bauer, Ph.D.†
Minneapolis, Minnesota

*Taranta, Angelo: Streptococcology for the Non-Streptococcologist. Minnesota Med 58:585, 1975.

†Director, Division of Medical Laboratories, Minnesota Department of Health.

Artificial Heart

Drs. Kletschka and Rafferty* are to be congratulated for their persistence in developing a blood propelling mechanism with notably low degrees of hemolysis when tested in vitro and laboratory animals. Although the roller pump has been a reliable and efficient mechanism for providing nonpulsatile flow during temporary extracorporeal circulation, the centrifugal pump may, indeed, be a significant step toward developing long term pumping for an artificial heart.

Low levels of red blood cell destruction have been clearly demonstrated by in vitro experimentation. Other limiting factors in appropiate blood-pump interface surfaces will be critical for long term pumping. One might speculate on the long term implications of nonpulsatile flow in a physiologic setting. In the usual establishment of temporary extracorporeal circulation for currently employed operable heart lesions, the degree of hemolysis occurring in the roller type pump has been well demonstrated to be at acceptable levels.

Whether the centrifugal pump has application clinically in the common adult procedures is yet to be demonstrated. For long term temporary support or perhaps in very small patients, this low degree of hemolysis could provide an added degree of safety. In either event, substantial clinical trial will be required to assess these factors.

Joseph Kiser, M.D.
Minneapolis, Minnesota

*See page 757.

MSMA ANNUAL MEETING

To Build a Meeting . . .

Details are the mortar in the building of a successful meeting. Perhaps with the appointment of Local Arrangements Committee members we should issue a trowel because this committee concerns itself with the innumerable details of the MSMA Annual Meeting.

The Local Arrangements Committee will organize groups of physicians to welcome out of town guests and program participants and provide transportation for them during their stay in Rochester. Entertainment, theme, and a myriad of provisions for the President's Reception and Annual Banquet will be arranged by the Committee. In addition, members will determine course and court facilities for golf and tennis tournaments, coordinate meeting publicity with the state office and disseminate this information through local media. Securing registration manpower from the Chamber of Commerce and supplying attendees with information on tours, sightseeing, shopping, etc. will be necessary details also.

A most important meeting detail is selecting a Local Arrangements chairman. This year's is Doctor John Mayne. Not unfamiliar with Annual Meeting preparations (he has served as chairman and currently is a member of the Scientific Assembly Committee), John has a number of embellishments ready for the 1976 Meeting. One is a Friday afternoon guaranteed to bring the Meeting to a convivial close! But more details on that and other segments of the Meeting later . . .

R. D. Semsch, M.D.
Chairman
Scientific Assembly

Letter to the Editor

Psychotic Child and Mentally Retarded Child

Dear Editors:

I am writing to take issue with the article by Dr. Robert H. Olin, entitled, "Differentiating the Psychotic Child from the Mentally Retarded Child," which appeared in the June, 1975, issue of MINNESOTA MEDICINE.*

My basic disagreement from an eclectic point of view is that the article has a marked psychoanalytic orientation. There is good evidence in the literature that autism is most likely an organic impairment of brain tissue rather than a psychological condition in its etiology. When Kanner, in 1943, described the parents of the autistic children, he initially referred to some of the parents being colder and less responsive. Statistics and articles that have followed the course of autistic children and their parents have not found that the parents are different in this respect than from other parents studied. Autism is different from schizophrenia in that it is almost unheard of to have hallucinations in an autistic child. Most autistic children have a prognosis based on the ability to speak meaningful words by age five and having an IQ that is adequate to allow them to function in a better fashion. Most autistic children have very low IQs and do not have speech. In the followup studies by Kanner, and others, only a small percentage of autistic children become functioning adults.

Another issue that I disagree with is that people vacillate between autism and schizophrenia or other psychotic-like illnesses. Certainly there are conditions in childhood that are so difficult to diagnose that one is hard put to put a label on them. Nevertheless the purely autistic child doesn't cross into schizophrenia as an adult. Loretta Bender's follow-up studies of schizophrenic children do on the other hand show that most of them turn out to be schizophrenic adults.

In a young child, when one is faced with the differential diagnosis of psychosis or mental retardation, my general experience has been that retarded children who are mildly to moderately retarded try to relate and are much warmer and more in contact with what's going on around them in spite of the fact that their intellectual abilities are lower. I have found this a very useful criterion, although at times as mentioned previously, one is faced with a situation where one is dealing with both psychosis and with retardation. Although this is less common in general practice, it is not rare in the practice of child psychiatry.

*Pages 489-492.

Joel Finkelstein, M.D.
Minneapolis, Minnesota

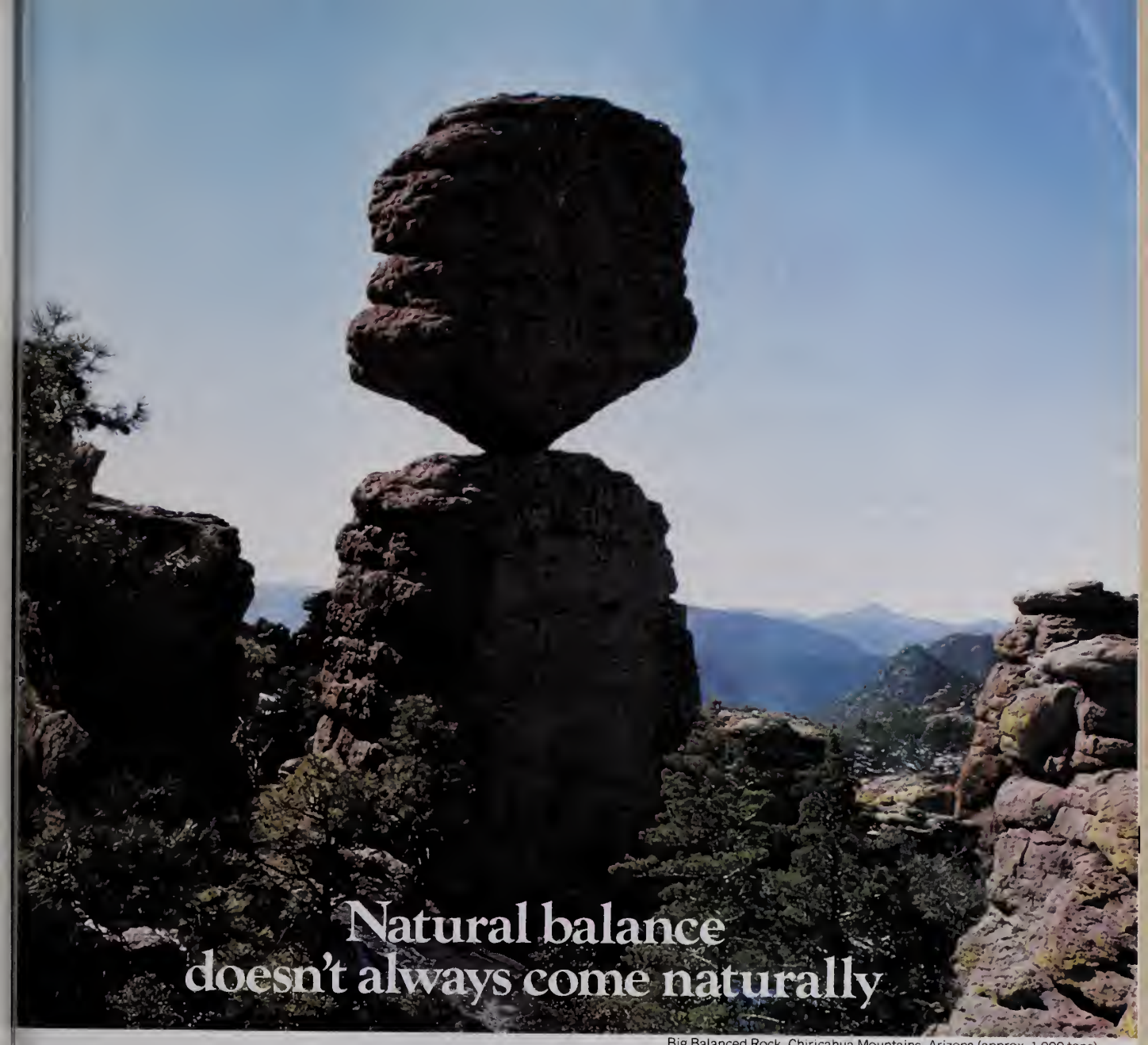
Allergic Reactions

Again, this year I am compiling case reports of allergic reactions to biting insects, i.e., mosquitoes, fleas, gnats, kissing bugs, bedbugs, chiggers, black flies, horseflies, sandflies, deerflies, etc.

I would like physicians to supply me with case reports of those patients who have had reactions to such insects. Include in your reports, the type of reaction and complications, if any, the age, sex, and race of the patient, the site of the bite(s), the season of the year, the immediate symptoms, the skin test results, desensitization results, if any, and any associated other allergies. Send this information to the following address:

Claude A. Frazier, M.D.
4-C Doctors' Park
Asheville, NC 28801

Claude A. Frazier, M.D.



Big Balanced Rock, Chiricahua Mountains, Arizona (approx. 1,000 tons)

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lso available as Antivert (meclizine HCl) 12.5 mg. scored ets, for dosage convenience and flexibility.

ntivert/25 (meclizine HCl) 25 mg. *Chewable* Tablets for sea, vomiting and dizziness associated with motion sickness.

F SUMMARY OF PRESCRIBING INFORMATION

DICATIONS. Based on a review of this drug by the National Academy of ences—National Research Council and/or other information, FDA has classified indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with tion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the tibular system.

Final classification of the less than effective indications requires further estigation.

CONTRAINDICATIONS. Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

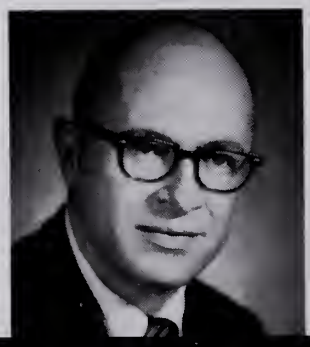
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Opinion & Dialogue

Should a specially prepared package insert be made available to patients?



Dr. Alexander M. Schmidt
Commissioner,
Food and Drug
Administration



Dr. James H. Sammons
Executive Vice President
of the American
Medical Association

The idea of a so-called patien package insert has been around fc a long time. Many physicians alrea use written instruction sheets to provide patients with information about the drugs they are taking. Ar some physicians give verbal instru tions; but in too many instances these are what I call eye-glazing ex ercises. I have seen patients sit wit glazed eyes listening to a rapid-fire lecture by a hurried physician whc has 20 people out in his waiting room. These patients aren't given sufficient understanding and ther fore do not follow instructions. So think the idea of an official packag insert for patients is a good one. Perhaps we should really think of this kind of information simply as extension of drug labeling.

The benefits of patient involvemen

Many physicians may not rea ize how frequently a patient obtair his drug information from Aunt Tillie or the next door neighbor. Ar this information is almost always bad or irrelevant to the case at har Furthermore, the incentive to go along with a prescribed program i slim if the only reading matter the patient receives, along with his pr scription, is a bill.

As an educator I am impress by the principle that the best way t get someone to do something is to involve him in the process. So the

I think there are advantages well as some real disadvantages ir a patient package insert. When yo begin to use semi-medical or med cal terms to describe complicatio or possible sequelae of disease or treatment, you may frighten the p tient—particularly since the more highly sophisticated patient is not the one who is going to read the in sert. The patient who will read it is the one most susceptible to fright and confusion by the language.

On the positive side, a packa insert will probably give the patier better insight into why he is being treated the way he is, and it may give the physician a little bit more time. But it does not remove from the physician the need or obligati to explain the insert.

Some pitfalls in the inclusion of side effects

Certainly a patient should be warned of the possibility of seriou side reactions—to know what the real dangers are. But it doesn't do bit of good to indicate that a patie on oral penicillin may develop a rash, itching, or a drop in blood pressure. Or that he may faint. I think the real danger is that fright engendered by the insert may pos sibly outweigh the potential good.

main purpose of drug information for the patient is to get his cooperation in following a drug regimen.

Preparation and distribution of patient drug information

We would hope to amass information from physicians, medical societies, the pharmaceutical industry and centers of medical learning. The ultimate responsibility for uniform labeling must, however, rest with the Food and Drug Administration. There is nothing wrong with this agency saying, "this information is generally agreed upon and therefore it should be used," as long as our process for getting the information is sound.

Distribution of the inforrnation is a problem. In great measure it would depend on the medication in question. For example, in the case of an injectable long-acting progesterone, we would think it mandatory to issue two separate leaflets—a short one for the patient to read before getting the first shot and a long one to take home in order to make a decision about continuing therapy. In this case, the information might be put directly on the package and not removable at all. But for a medication like an antihistamine this information might be issued separately, thus giving the physician the option of distribution. This could preserve the placebo use, etc.

It is in the distribution of patient information that the pharmacist may get involved. As professionals and members of the health-care team and as a most important source of drug information to patients, pharmacists should be responsible for keeping medical and drug records on patients. It is also logical that they should distribute drug information to them.

Realistic problems must be considered

We have to expect that the introduction of an information device will also create new problems. First, how can we communicate complex and sophisticated information to people of widely divergent socioeconomic and ethnic groups? Second, what will we say? And third, how can we counteract the negative attitude of many physicians toward any outside influence or input? Hopefully the medical profession will respond by anticipating the problems and helping to solve them. Assuming we can also solve the difficulty of communicating information to diverse groups throughout the United States, our remaining task will be the inclusion of appropriate material.

What information is appropriate?

In my opinion, technical, chemical and such types of material should not be included. And there is no point in the routine listing of side effects like nausea and vomiting which seem to apply to practically all drugs, unless it is common with the drug. However, serious side effects should be listed, as should information about a medication that is potentially risky for other reasons.

Other pertinent information might consist of drug interactions, the need for laboratory follow-up, and special storage requirements. What we want to include is information that will help increase patient compliance with the therapy.

Positive aspects of patient drug information

Labeling medication for the patient would accomplish a number of good things: the patient could be on the lookout for possible serious side effects; his compliance would increase through greater understanding; the physician would be a better source of information since he would be freer to use his time more effectively; other members of the health-care team would benefit through patient understanding and cooperation; and, finally, the physician-patient relationship would probably be enhanced by the greater understanding on the part of the patient of what the physician is doing for him.

Only the doctor can remove that fear by 20 or 30 minutes of conversation.

I'm not suggesting that we withhold any information from the patient because, first of all, it would be totally dishonest and secondly, it would defeat the very purpose of the insert. I do think that a patient on the birth control pill should know about the incidence of phlebothrombosis.

If you're going to tell a patient the incidence of serious adverse reactions, then you have to tell him that a concerned medical decision was made to use a particular medication in his situation after careful consideration of the incidence of complications or side effects.

Emotionally unstable patients pose a special problem

There are patients who, because of severe emotional problems, could not handle the information contained in a patient package insert. Yet if we are going to have a package insert at all, we just can't have two inserts. I think we might simply have to tell the families of these patients to remove the insert from the package.

Legal implications of the patient package insert

Just what effect would a patient package insert have on malpractice? We could try to avoid any legal implications by pointing out that the physician has selected a particular medication because, in his professional judgment, it is the treatment of choice. For instance, you can't tell everyone taking antihistamines not to work just because a few patients develop extreme drowsiness which can lead to accidents. And what about the very small incidence of aplastic anemia rarely associated with chloramphenicol? If, based on sensitivity studies and other criteria, we decide to employ this particular antibiotic, we do so in full knowledge of this serious potential side effect. It's not a simple problem.

How do we handle an insert for medication used for a placebo effect?

With rare exceptions, physicians no longer use medications for a placebo effect. This question does raise the issue of how a patient may react to receiving a medication without a package insert.

Preparation of the package insert

The development of the insert ought to be a joint operation between physicians, the pharmaceutical industry, the A.M.A. and the F.D.A.

I view the A.M.A.'s role as a coordinator or catalyst. It is the only organization through which the profession as a whole, irrespective of specialty, can speak. It has relatively instant access to all the medical expertise in this country. And it can bring that professional expertise together to ensure a better package insert. The A.M.A. can work in conjunction with the industry that has produced the product and which is ultimately going to supply the insert.

I don't think we should rely, or expect to rely, on legislative committees and their nonprofessional staffs to make these decisions when it is perfectly within the power of the two groups to resolve the issues in the very best American tradition—without the government forcing us to do it. I think the F.D.A. has to be involved, but I'd like them to become involved because they were asked to become involved.

Pharmaceutical Manufacturers Association
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* **Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired. Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricem and gout, reversible nitrogen retention, decreasi alkali reserve with possible metabolic acidosis, hyp glycemia and glycosuria (diabetic insulin requi ments may be altered), digitalis intoxication (hypokalemia). Use cautiously in surgical patien Concomitant use with antihypertensive agents m result in an additive hypotensive effect. 'Dyazic interferes with fluorescent measurement quinidine.

Adverse Reactions: Muscle cramps, weakness, d ziness, headache, dry mouth; anaphylaxis; ras urticaria, photosensitivity, purpura, other derm tological conditions; nausea and vomiting (may i dicate electrolyte imbalance), diarrhea, constipatic other gastrointestinal disturbances. Necrotizi vasculitis, paresthesias, icterus, pancreatiti xanthopsia and, rarely, allergic pneumonitis ha occurred with thiazides alone.

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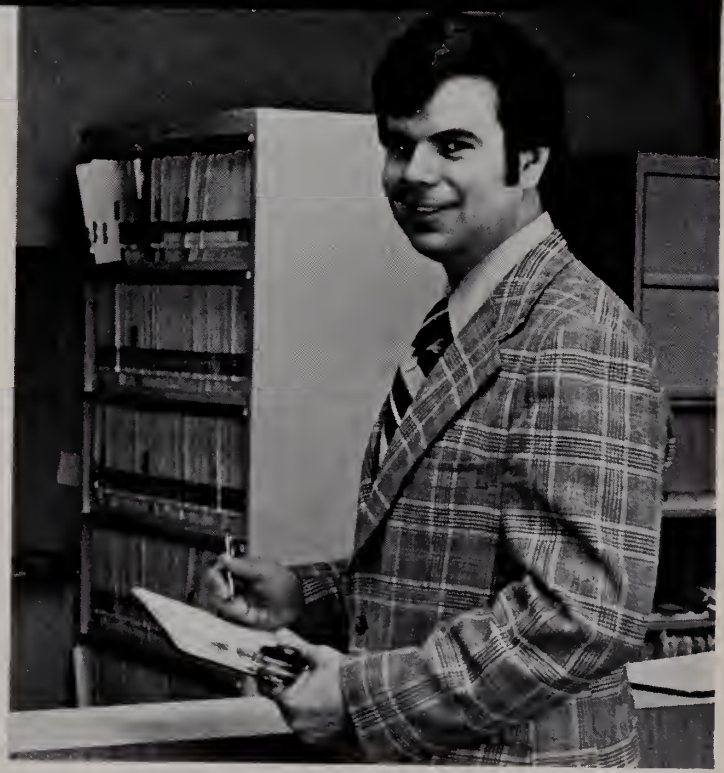
Scott Froehlich helps make your claims preparation more efficient.

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Special Article

Artificial Heart

III. Development of Efficient Atraumatic Blood Pump. A Review of the Literature Concerning in Vitro Testing of Blood Pumps for Hemolysis.

HAROLD D. KLETSCHKA, M.D.*; EDSON H. RAFFERTY, B.S. (MECH. ENG.), CCE*;
DOUGLAS A. OLSEN, Ph.D.*; E. W. CLAUSEN, CMfg.E*;
LLOYD C. HUBBARD, B.S. (ELEC. ENG.)*; ALLAN R. ROBINSON, CCP*;
WAYNE H. LARSON, B.S.*

A review of the world literature reveals the BIO-MEDICUS RAFFERTY/KLETSCHKA artificial heart pump operating on the constrained force-vortex principle to be the most atraumatic blood pump in existence. The development of this efficient atraumatic blood pump has overcome the most formidable barrier to the successful attainment of an artificial heart. Immediate clinical and experimental use of this pump for extracorporeal short-term and long-term applications is envisioned.

SUCCESSFUL DEVELOPMENT of an artificial heart requires solutions to problems concentrated in the following five major categories: (1) pumping mechanism; (2) materials; (3) regulatory requirements; (4) pump drive system; (5) power requirements.

Progress has been made in each area through independent efforts of many investigators. However, potential success in developing a totally implantable artificial heart to replace the natural heart has to be viewed from the standpoint of the interdependency of the various separate factors bearing on the problem as a whole. In adopting this "total concept" approach, our group made the judgment that the key to achieving an artificial heart within the limitations of present day technology would reside in the development of an efficient atraumatic blood pump. A blood pump exhibiting those characteristics has now been developed by us. It is the purpose of this paper to present the performance of this unit and to compare its blood handling qualities with those of other blood pumps. Availability of an efficient atraumatic blood pump should greatly simplify the solution to the other problems associated with materials, regulatory systems, pump drive system, and power requirements in fashioning an ultimate artificial heart.

*Bio-Medicus, Inc., 15307 Industrial Road, Minnetonka, Minnesota.

See editorial, page 749.

We feel that with the successful development of this efficient atraumatic blood pump we have overcome the most significant obstacle to the attainment of what is ultimately desired in the way of an implantable, autonomously operational artificial heart. It follows as a natural corollary that the blood pump can also more immediately find application advantageously as the component of cardiac assist devices and heart-lung machines.

Although centrifugal pumps have heretofore been noted for their destructive qualities,[1-5] they possess the attributes of high pumping efficiencies and performance characteristics analogous to those of the mammalian heart.[2,5,6] Through employment of a revolutionary new centrifugal pumping method known as the Constrained Force-Vortex Principle, it has become possible for us to utilize these advantages while rendering the pump very atraumatic in handling blood.[5,7] Once the soundness of the basic pumping principle was demonstrated, the device underwent several modifications in an attempt to improve its efficiency and capabilities for handling blood atraumatically. The performance of the pump has been improved by these changes to such an extent that models are now available which can pump blood atraumatically, even under supercritical conditions. The conditions are referred to as supercritical because circulation of the blood by the pump was carried out: (1) in an in vitro environment; (2) at a

temperature of 37° C.; (3) at flow rates greatly in excess of physiological requirements; (4) against mean pressures approximately twice the physiological normal level; (5) using horse blood; (6) at times using pre-lysed horse blood.

Methodology

Freshly drawn horse blood was collected in a sterile plastic polyvinyl pump bag containing heparin. A sterile control bag was filled with blood from the pump bag. Although of much smaller capacity, the control bag possessed approximately the same surface to volume ratio as that found in the pump bag. The pump and control bags were placed in a water bath maintained at 37° C. throughout the course of the experiment.

After connecting the pump to the pump bag, circulation of the blood was carried out in a closed system of approximately five liters capacity. The polyvinyl control bag was gently rotated from time to time to ensure adequate mixing of the blood elements.

Flow rates were determined either from calibration curves using horse blood, or measured directly with an in-line Biotronex flow probe (Model No. BLX-2159) and Biotronex flowmeter (Model No. BL-615). *Pump pressures* were either calculated from calibration graphs using horse blood, or were measured directly with Biotronex pressure probes (Model No. BL 9630) placed in both the inlet and outlet lines and attached to Biotronex pressure meters (Model No. BL-635). *Revolutions per minute* were measured by means of a calibrated generator tachometer, a General Radio Strobotach, or a digital tachometer.

Blood samples for appropriate tests were drawn at approximately the same time from the control and pump bags prior to initiating circulation and at periodic intervals thereafter.

In those experiments in which pre-lysed horse blood was used, lysis was effectuated by admixture of air with the blood at the time it was drawn from the animal. Additional lysis carried out thereafter during a given experiment was achieved by roughly agitating the blood.

Results and Analysis

Testing results of the Bio-Medicus Rafferty/Kletschka Nonpulsatile Artificial Heart Blood Pump from a group of selected experiments are tabulated in Table 1. The experimental design of the testing program incorporated flow rates from 3 to 25 L./min and pump pressures up to 198 mm Hg. Complete absence of hemolysis characterizes the results of the experiments even though the blood was circulated under very severe test conditions.

The index of hemolysis* is regarded as an expression of the general blood handling qualities of a pump.[8-12] Studies we have done corroborate this view. For example, no demonstrable changes in our pump bag samples over those taken from the control bag in tests ranging over circulation periods of 18-48 hours were detected with respect to values for white cell counts, platelet counts, blood urea nitrogen, uric acid, total protein,

*Index of hemolysis is defined as the grams of hemoglobin liberated per 100 liters of blood pumped.

TABLE 1
In Vitro Testing
Bio-Medicus Rafferty/Kletschka Blood Pump*

Pump Description	Pump Type	Blood Source	Temperature	System Priming Volume (Liters)	Rpm	Flow Rate (L./Min.)	Circul on Tim (Hou
Constrained Force-Vortex	Model 100 Series	Horse	37° C.	5	1500-2500	11.9-13.85	2 15 0
Constrained Force-Vortex	Model 100 Series	Horse-Prelysed	37° C.	5.5	1500-2500	11.05-20	2 55 0
Constrained Force-Vortex	Model 200 Series	Horse-Prelysed	37° C.	5.5	1500-2500	9-15.8	1 55 0
Constrained Force-Vortex	Model 200 Series	Horse-Prelysed	37° C.	5.5	1500-2500	9-15.8	1 54 0
Constrained Force-Vortex	Model 200 Series	Horse	37° C.	5.5	1000-2500	6-15.8	5 52 /6
Constrained Force-Vortex	Model 200 Series	Horse	37° C.	5.14	2000	6	1 10 0
Constrained Force-Vortex	Model 200 Series	Horse	37° C.	4.73	1000-2500	5.4-14.5	4 3/(
Constrained Force-Vortex	Model 200 Series	Horse	37° C.	4.56	1500-2500	7-15.8	4 48 0
Constrained Force-Vortex	Model 200 Series	Horse	37° C.	4.61	500-1400	8.5-24.6	3 55 0
Constrained Force-Vortex	Model 200 Series	Horse	37° C.	4.27	1500-2500	9-25	48 1/(
Constrained Force-Vortex	Model 200 Series	Horse	37° C.	4.62	3000-3500	3-8.3	1 7/(
Constrained Force-Vortex	Model 200 Series	Horse	37° C.	3.805	1000-1500	6.1-12.39	7 15 /(

* = Manufactured by Bio-Medicus, Inc., 15307 Industrial Road, Minnetonka, Minnesota 55343
□ = Mean values

albumin, total bilirubin, SGOT, LDH, inorganic phosphorous, cholesterol, or alkaline phosphatase.

We have selected a 5 liter priming volume for our tests for the following reasons:

1. Repeated samplings have a relatively small effect on the circulating volume.
2. The surface area provides for efficient heat exchange in the water bath.
3. To provide an adult "physiological" circulating blood volume. The necessity of extrapolating results to the ultimate intended environment is thereby obviated.

In comparing pumps, calculations based on hemolysis per passage through the pump correct for any artifacts arising from use of various prime volumes by different investigators since the amount of hemolysis bears a direct linear relationship to the number of passages the prime volume of blood makes through a given pump.[1,13-17]

Discussion

Pumps

Encouraged by our success in developing an atraumatic pump, we were prompted to compare its performance to other blood pumps. A review of the world literature was undertaken in which the hemolysis data and experimental conditions for pumps of all categories, which had been subjected to in vitro testing, were compiled. These tabulations are detailed in Tables 2-8. The large number of pumps represented in the multiple tables is a reflection of the widespread, serious attempts that have been made over many years by various groups around the world to develop an atraumatic blood pump. Certain general observations gained from reviewing the Tables are of interest.

Ventricle and Diaphragm Pumps

There is widespread belief that ventricle type pumps are the most atraumatic of the blood pumps.[27,68,69] It seems this view stems from the similarity of this type pump to that of the natural heart rather than objective experimental pumping data. In any event, most investigators working on artificial heart programs seem to have favored this type pump or another closely related to it, the diaphragm pump. A critical comparison with other pumps, however, reveals many pumps in other categories to be more atraumatic. In fact, some of the diaphragm and ventricle pumps appear marginal as to their atraumatic pumping qualities even though clinical application and some long-term animal survivors have taken place using such units as heart assist or artificial heart pumps. Considering other problems inherent in these pumps such as those related to valves, repeated flexing of materials, low pumping efficiencies, etc., it seems they are less than ideal.

Finger, Roller, and Piston Pumps

Although the finger pump found early acceptance for use in heart-lung machines, their relatively traumatic blood handling properties soon became recognized. It was supplanted, therefore, when it was eventually discovered that blood trauma could be minimized in roller pumps by closely controlling the degree of occlusion of the rollers. The roller type pump gained in general popularity and today enjoys the position of being the most widely employed blood pump. However, even the roller pump is outperformed by other

TABLE 1 (continued)

Total Flow Liters)	Pump Pressure (mm. Hg)	Increase In Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
1737.15	20-62.5	0.000	0.000	0.000	Company Pump Reference No. CS−6.35NcT3HYTDEE72
2784	20-62.5	0.000	0.000	0.000	Company Pump Reference No. CS−6.35NcT3HYTDEE72
1167	53-61	0.000	0.000	0.000	Company Pump Reference No. MmS−6.35NcT3HYTMEE73
1189.2	53-61	0.000	0.000	0.000	Company Pump Reference No. MmA−6.35NcT3HYTMEE73
3607.1	49-61	0.000	0.000	0.000	Company Pump Reference No. MmA−6.35NcT3HYTMEE73
420	105	0.000	0.000	0.000	Company Pump Reference No. MmS+6.35NcT3SYTMEE73
2743	53-70	0.000	0.000	0.000	Company Pump Reference No. MmS+6.35NcT3SYTMEE73
3318.4	61-89	0.000	0.000	0.000	Company Pump Reference No. MmS+6.35NcT3SYTM-EE74
3933	45-103	0.000	0.000	0.000	Company Pump Reference No. MmS−12.7NcT3SYTMEE74
7849	53-89	0.235/Hr.□	0.0018□	0.001	Company Pump Reference No. MmS+6.35NcT3SYTM-EE74
227	180-198	0.000	0.000	0.000	Company Pump Reference No. MmS+6.35NcT3SYTcM-EE74
3694.1	30-70	0.000	0.000	0.000	Company Pump Reference No. MmS+7.87NcT3SYTM-EE75

TABLE 2
In Vitro Testing
Pulsatile Pumps—Roller Type

Source	Pump Description	Number of Rollers	Blood Source	Temperature	Setting	System Priming Volume (Liters)	RPM	Flow Rate (L./Min.)	Circulation Time (Hours)	Pr Pre (mn
Dennis, et al.[18] (1951)	1 7/32" diameter roller	2				0.2	100	0.199		100 C
	1 8/32" diameter roller	2				0.4	100	0.551		100 C
	1 9/32" diameter roller	2				0.35	100	0.580		100 C
	1 10/32" diameter roller	2				0.4	100	0.582		100 C
Khayutin[19] (1958)		3	Human			0.1		0.120	2/3	
	Race bearing compression of annular tube, rotated by an eccentric.	1	Human			0.1		0.120	2/3	
	Race bearing compression of annular tube, rotated by an eccentric.	1	Human			0.1		0.120	1	
	Race bearing compression of annular tube, rotated by an eccentric.	1	Human			0.1		0.060	1.5	
Leonards, et al.[20] (1958)	DeBakey	2	Canine		Just occlusive	1.5		3	1	
	DeBakey	2	Canine		Just occlusive	1.5		3	1/3	
	DeBakey	2	Human		Just occlusive	2.0		3	1	
Kirby[21] (1958)	Mark Co.	2			Occlusive					
McCaughan, et al.[9] (1958)	Mark-DeBakey	2	Canine		Occlusive	1.3		0.625	1	
	Mark-DeBakey	2	Canine		Occlusive	1.3		1.5	1	
	Mark-DeBakey	2	Canine		Occlusive	1.3		1.75	1	
	Mark-DeBakey	2	Canine		Occlusive	1.3		1.825	1	
	Mark-DeBakey	2	Canine		Occlusive	1.3		3.7	1	
	Mark-DeBakey	2	Canine		Occlusive	1.3		5.6	1	
	Mark-DeBakey	2	Canine		Occlusive	1.2	94	3.6	1	
	Mark-DeBakey	2	Canine		Partial occlusive	1.2	252	3.6	1	
	Mark-DeBakey	2	Canine		Partial occlusive	1.2	150	3.6	1	
	Mark-DeBakey	2	Canine		Partial occlusive	1.2	118	3.6	1	
	Mark-DeBakey	2	Canine		Occlusive	0.5		1.75	1	
	Mark-DeBakey	2	Canine		Occlusive	0.620		1.75	1	
	Mark-DeBakey	2	Human		Occlusive	1.2		3.0	1	470
	Mark-DeBakey	2	Human		Nonocclusive	2.5		3.0	1	470
Hodges, et al.[22] (1958)	Mark II	2	Canine		Occlusive	0.5		1.5	2	275
	Mark II	2	Canine		Nonocclusive	0.5		1.5	2	275
	Mark II	2	Canine		Occlusive	0.5		1.5	2	275
	Mark II	2	Canine		Nonocclusive	0.5		1.5	2	275
	Mark II	2	Canine		Occlusive	0.5		1.5	2	200
	Mark II	2	Canine		Nonocclusive	0.5		1.5	2	200
Breckler, et al.[10] (1959)	DeBakey (Salisbury Design)	2	Canine			0.8		3	2	
	DeBakey (Salisbury Design)	2	Canine			1.0		2.4	2	
	DeBakey (Salisbury Design)	2	Canine			0.8	48	3	1	
Cahill, et al.[23] (1959)	Leonards	2	Human	25°-28.5°C.	Occlusive	0.5-0.6		0.2-0.215	19 (E)	80/
	Hercik		Human	25°-28.5°C.	Nonocclusive	0.5-0.6		0.2-0.215	13 (E)	80/
	Hercik		Human	25°-28.5°C.	Nonocclusive	0.5-0.6		0.2-0.215	11 (E)	80/
Head, et al.[24] (1960)	Pemco-DeBakey	2	Canine		Nonocclusive+	1.5	50	2.0		410/
	Pemco-DeBakey	2	Canine		Just non-occlusive++	1.5	23	2.0		400/

E = Estimated from Authors' Data.
C = Calculated from Authors' Data.
* = Assuming Hematocrit of 40.
T = Total Hemoglobin (MGM.)
+Nonocculsive = 300 cc./Min. Back Flow at 36" Hydrostatic Pressure.
++Just Nonocclusive = No Back Flow at 36" Hydrostatic Pressure.
ΔTight Occlusive = No Back Flow At Any Arterial Line Pressure.

TABLE 2 (continued)

Increase In Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
min.	0.36 (C)	0.402	Recalculated I.H.: 0.214 (C)*
min.	0.436 (C)	0.435	Recalculated I.H.: 0.26 (C)*
min.	1.113 (C)	1.113	Recalculated I.H.: 0.67 (C)*
min.	0.672 (C)	0.673	Recalculated I.H.: 0.40 (C)*
U./40 min. (C)	0.27 rel. U. % HGB. (C)		Closed system
U./40 min. (C)	0.08 rel. U. % HGB. (C)		Closed system
U./hr. (C)	0.19 rel U. % HGB. (C)		Closed system
rel U./hr. (C)	0.13 rel. U. % HGB. (C)		Closed system
ır. (E)		0.008 (E) (C)*	
/20 min. (E)		0.21 (E) (C)*	14 F. catheter line constriction
/hr. (E)		0.36 (E) (C)*	Human blood outdated
			43 milligrams per cent hemolysis
(T)	0.24 (C)*	0.144 (C)	Closed system
(T) (E)	0.25 (E) (C)*	0.151 (C)	Closed system
(T) (E)	0.22 (E) (C)*	0.13 (C)	Closed system
(T) (E)	0.19 (E) (C)*	0.112 (C)	Closed system
(T) (E)	0.41 (E) (C)*	0.245 (C)	Closed system
(T) (E)	0.49 (E) (C)*	0.292 (C)	Closed system
(T) (E)	0.33 (E) (C)*	0.196 (C)	Closed system
(T) (E)	0.02 (E) (C)*	0.012 (C)	Closed system
(T) (E)	0.04 (E) (C)*	0.024 (C)	Closed system
(T) (E)	0.17 (E) (C)*	0.1 (C)	Closed system
(T)	0.20 (E) (C)*	0.122 (C)	Heparinized blood used
(T)	0.2 (E) (C)*	0.118 (C)	ACD blood used
(T)	0.65 (E) (C)*	0.39 (C)	
(T)	0.17 (E) (C)*	0.103 (C)	
ırs.	0.16 (C)	0.097 (C)*	27 CC. stroke volume
ırs.	0.11 (C)	0.068 (C)*	27 CC. stroke volume
ırs.	0.66 (C)	0.397 (C)*	27 CC. stroke volume
ırs.	0.62 (C)	0.124 (C)*	27 CC. stroke volume
ırs.	0.23 (C)	0.137 (C)*	27 CC. stroke volume
ırs.	0.25 (C)	0.152 (C)*	27 CC. stroke volume
ırs.	0.138 (C)	0.138	No line constriction
ırs.	0.21 (C)	0.173	Recalculated I.H.: 0.208 (C). ¼ inch line constriction
	0.111 (C)	0.111	No line constriction
ır.	≅0.1-0.135 (C)	≅0.064-0.08 (C)*	¾ inch rubber tubing between roller and plate
ır. (E) (C)	≅0.11-0.145 (E) (C)	≅0.067-0.087 (C)*	¾ inch I.D. polyvinyl chloride tubing
ır.	≅0.19-0.245 (C)	≅0.114-0.147 (C)*	½ inch I.D. polyvinyl chloride tubing
	0.045	0.027 (C)*	20 CC. stroke volume. ¾" pump chamber. No. 10 cannula
	0.054	0.032 (C)*	42 CC. stroke volume. ¾" pump chamber. No. 10 cannula

(continued)

TABLE 2 (continued)
In Vitro Testing
Pulsatile Pumps—Roller Type (Cont.)

Source	Pump Description	Number of Rollers	Blood Source	Temperature	Setting	System Priming Volume (Liters)	RPM	Flow Rate (L./Min.)	Circulation Time (Hours)
Head et al.[24] (Continued)	Pemco-DeBakey	2	Canine		Tight occlusive[Δ]	1.5	21	2.0	
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	33	2.0	
	Pemco-DeBakey	4	Canine		Just nonocclusive	1.5	41	2.0	
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	24	2.0	
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	76	2.0	
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	39	2.5	
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	31	2.5	
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	22	2.5	
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	20	1.675	1
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	60	4.44	1
	Pemco-DeBakey	4	Canine		Just nonocclusive	1.5	20	1.19	1
	Pemco-DeBakey	4	Canine		Just nonocclusive	1.5	60	3.366	1
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	60	3.95	1
	Pemco-DeBakey	2	Canine		Just nonocclusive	1.5	60	2.36	1
Akutsu, et al.[25] (1960)	Roller traveling on 2 polyurethane ventricles; 2 valves.	1	Human	Room	Occlusive	1.5	100	1.1	1
	Roller traveling on 2 polyurethane ventricles; 2 valves.	1	Human	Room	Occlusive	1.5	100	1.1	1
Akutsu, et al.[26] (1960)	2 polyurethane ventricles	1	Human						
Cappelletti, et al.[14] (1961)	Mark-DeBakey	2	Canine			1.0		0.92	1
	Mark-DeBakey	2	Canine			1.250		2.166	1
Esmond, et al.[27] (1961)	Clinical Perfusion Associates, Inc. pump	1	Canine			0.958		4	2
	Clinical Perfusion Associates, Inc. pump	1				0.660		4	1
Brown, et al.[28] (1961)	Hercik		Human		Nonocclusive	"Small Volume"	36	2	2
Pierson, et al.[29] (1962)	Goodyear—2-4 rollers		Canine		Partially occlusive	1.5-2		2	1
	Goodyear—2-4 rollers		Canine		Partially occlusive	1.5-2		2	1
Cappelletti, et al.[15] (1962)	Mark-DeBakey	2	Canine		Nonocclusive	1		0.920	1
	Mark-DeBakey	2	Canine		Nonocclusive	1.250		2.166	1
Domingo, et al.[16] (1963)	NIH		Canine					6	1
	NIH		Canine					3	1
	NIH		Canine					1	1
	Wesolowski	1	Canine					6	1
	Wesolowski	1	Canine					3	1
	Wesolowski	1	Canine					1	1
	Wesolowski	1	Canine					6	1
	Wesolowski	1	Canine					3	1
	Wesolowski	1	Canine					1	1
	Wesolowski	1	Canine					6	1
	Wesolowski	1	Canine					3	1
	Wesolowski	1	Canine					1	1
	Wesolowski	1	Canine					6	1
	Wesolowski	1	Canine					3	1
	Wesolowski	1	Canine					1	1
	Wesolowski	1	Canine					6	1
	Wesolowski	1	Canine					3	1
	Wesolowski	1	Canine					1	1
	NIH		Canine					6	
	NIH		Canine					3	
	NIH		Canine					1	

TABLE 2 (continued)

ump ressure m. Hg.)	Increase In Plasma HGB. (MGM. % Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
0/180		0.090	0.054 (C)*	48 CC. stroke volume. ¾" pump chamber. No. 10 cannula
0/190		0.040	0.024 (C)*	30 CC. stroke volume. ½" pump chamber. No. 10 cannula
0/150		1.0	0.6 (C)*	12 CC. stroke volume. ½" pump chamber. No. 10 cannula
0/200		0.06	0.036 (C)*	42 CC. stroke volume. ¾" pump chamber. No. 10 cannula
0/200		0.5	0.3 (C)*	13 CC. stroke volume. ⅜" pump chamber. No. 10 cannula
0/390		0.4	0.24 (C)*	32 CC. stroke volume. ⅝" pump chamber. No. 10 cannula
0/30		0.3	0.18 (C)*	40 CC. stroke volume. ⅝" pump chamber. No. 6 cannula
0/40		0.4	0.24 (C)*	57 CC. stroke volume. ⅝" pump chamber. No. 10 (2) cannula
	32/hr.	0.48	0.29 (C)*	No cannula
	66/hr.	0.4	0.24 (C)*	No cannula
	33/hr.	0.79	0.47 (C)*	No cannula
	141/hr.	1.0	0.6 (C)*	No cannula
/112	37/hr.	0.3	0.18 (C)*	No. 6 cannula
/440	33/hr.	0.4	0.24 (C)*	No. 10 cannula
CM. blood	30/hr.	0.68 (C)	0.48 (C)*	Left heart pump
CM. blood	30/hr.	0.68 (C)	0.38 (C)*	Right heart pump
	30/hr.			Rate of hemolysis essentially the same for the greater and lesser circulations
120	10.7/hr.	0.19 (C)	0.55	Recalculated I.H.: 0.116 (C)* . #14 F. line catheter
120	24.8/hr.	0.24 (C)	0.37	Recalculated I.H.: 0.143 (C)* . #14 F. line catheter
150	16.8/2 hrs.	0.03 (C)	0.037	Recalculated I.H.: 0.02 (C)* . Vinyl tubing
150	46/hr.	0.13 (C)	0.12	Recalculated I.H.: 0.08 (C)* . Latex tubing
CM. blood	0.041 MGM./L./30 min.		0.004	
iological"			0.288	Input pressure of 20 mm. Hg
iological"			0.170	Input pressure of 20 mm. Hg
120	10.7/hr.	0.194 (C)	0.193	Recalculated I.H.: 0.116 (C)* . #14 F. line catheter
120	24.8/hr.	0.238 (C)	0.238	Recalculated I.H.: 0.143 (C)* . #14 F. line catheter
120	500/hr. (T) (E)			
120	250/hr. (T) (E)			
120	75/hr. (T) (E)			
120	330/hr. (T) (E)			Roller + ring + bearings
120	175/hr. (T) (E)			Roller + ring + bearings
120	55/hr. (T) (E)			Roller + ring + bearings
120	300/hr. (T) (E)			Roller + gear
120	155/hr. (T) (E)			Roller + gear
120	45/hr. (T) (E)			Roller + gear
120	270/hr. (T) (E)			Roller only
120	130/hr. (T) (E)			Roller only
120	40/hr. (T) (E)			Roller only
120	250/hr. (T) (E)			Roller +ring + gear + bearing
120	120/hr. (T) (E)			Roller +ring + gear + bearing
120	35/hr. (T) (E)			Roller +ring + gear + bearing
120	185/hr. (T) (E)			Roller + ring + gear
120	100/hr. (T) (E)			Roller + ring + gear
120	30/hr. (T) (E)			Roller + ring + gear
				3.5 MGM. HGB. liberated/stroke (E)
				3.9 MGM. HGB. liberated/stroke (E)
				3.8 MGM. HGB. liberated/stroke (E)

– = Estimated from Authors' Data.
= Calculated from Authors' Data.
= Assuming Hematocrit of 40.
= Total Hemoglobin (MGM.)
= Assuming Hematocrit of 55 to Give Lowest I.H. Using Authors' Data.
Tight Occlusive = No Back Flow At Any Arterial Line Pressure.

TABLE 2
In Vitro Testing
Pulsatile Pumps—Roller Type (Cont.)

Source	Pump Description	Number of Rollers	Blood Source	Temperature	Setting	System Priming Volume (Liters)	RPM	Flow Rate (L./Min.)	Cir
Domingo et al.[16] (continued)	R-G		Canine					6	
	R-G		Canine					3	
	R-G		Canine					1	
	R-G-R		Canine					6	
	R-G-R		Canine					3	
	R-G-R		Canine					1	
	Wesolowski	1	Canine					5	
	Wesolowski	1	Canine					3	
	Wesolowski	1	Canine					1	
	Wesolowski	1	Canine					5	
	Wesolowski	1	Canine					3	
	Wesolowski	1	Canine					1	
	Wesolowski	1	Canine					5	
	Wesolowski	1	Canine					3	
	Wesolowski	1	Canine					1	
	Wesolowski	1	Canine					5	
	Wesolowski	1	Canine					3	
	Wesolowski	1	Canine					1	
Martin, et al.[30] (1964)	Kay-Anderson	2	Beef			0.520		3	2
	Hartford Triplex	1	Beef			0.740		3	4
Pierson, et al.[31] (1965)	Goodyear	4	Human			1.1		2	
Kusserow, et al.[32] (1965)	Conventional								
Bernstein, et al.[4] (1967)	Imico		Canine		Occlusive			2	
	Olson		Canine		Occlusive			2	
	Med-Science		Canine		Occlusive			2	
	Sarns		Canine		Occlusive			2	
	Olson		Canine		Occlusive			2	
	Olson		Canine		Nonocclusive			2	
	Imico		Canine		Occlusive			2	
	Imico		Canine		Nonocclusive			2	
	Sarns		Canine		Occlusive			2	
	Sarns		Canine		Nonocclusive			2	
	Sarns (Model 3500)		Canine		Occlusive			2	
Hoffman, et al.[33] (1970)	DeBakey-Pemco Model 1002.	2	Canine		Occlusive	0.700		2	
	Torque-motor-driven.	2	Canine		Occlusive	0.700		2	
	Pulsatile torque-motor-driven.	2	Canine		Occlusive	0.700		2	
	Pulsatile torque-motor-driven.	2	Canine		Occlusive	0.700		2	
	Pulsatile torque-motor-driven.	2	Canine		Occlusive	0.700		2	
Klain, et al.[34] (1970)	Pemco		Cow			2.5		5	
Hahn, et al.[35] (1973)	American Optical Co.	2	Bovine	10° C.	Partially occlusive	0.7	120 (E)	3	
	American Optical Co.	2	Bovine	10° C.	Partially occlusive	0.7	130 (E)	3	
	American Optical Co.	2	Bovine	10° C.	Partially occlusive	0.7	135 (E)	3	
	American Optical Co.	2	Bovine	19° C.	Partially occlusive	0.7	120 (E)	3	
	American Optical Co.	2	Bovine	19° C.	Partially occlusive	0.7	125 (E)	3	
	American Optical Co.	2	Bovine	19° C.	Partially occlusive	0.7	135 (E)	3	
	American Optical Co.	2	Bovine	28° C.	Partially occlusive	0.7	120 (E)	3	
	American Optical Co.	2	Bovine	28° C.	Partially occlusive	0.7	130 (E)	3	
	American Optical Co.	2	Bovine	28° C.	Partially occlusive	0.7	140 (E)	3	
	American Optical Co.	2	Bovine	37° C.	Partially occlusive	0.7	110 (E)	3	

TABLE 2 (continued)

Pump Pressure (m. Hg.)	Increase In Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
				2.7 MGM. HGB liberated/stroke (E)
				2.45 MGM. HGB liberated/stroke (E)
				1.75 MGM. HGB. liberated/stroke (E)
				1.25 MGM. HGB. liberated/stroke (E)
				1.4 MGM. HGB. liberated/stroke (E)
				1.1 MGM. HGB. liberated/stroke (E)
	300/hr. (T) (E)			1¼ inch diameter roller
	370/hr. (T) (E)			1¼ inch diameter roller
	130/hr. (T) (E)			1¼ inch diameter roller
	250/hr. (T) (E)			1 inch diameter roller
	160/hr. (T) (E)			1 inch diameter roller
	15/hr. (T) (E)			1 inch diameter roller
	305/hr. (T) (E)			⅞ inch diameter roller
	245/hr. (T) (E)			⅞ inch diameter roller
	125/hr. (T) (E)			⅞ inch diameter roller
	350/hr. (T) (E)			¾ inch diameter roller
	450/hr. (T) (E)			¾ inch diameter roller
	290/hr. (T) (E)			¾ inch diameter roller
00	77/2.9 hrs.	0.077	0.034 (C)◦	
00	49/4.1 hrs.	0.049	0.02 (C)◦	
	57/hr. (E)	0.52 (E) (C)	0.32	
				Produced consistently higher levels of plasma hemoglobin than a ventricle pump possessing an average hemolytic index of 0.08
			0.16	Tygon® tubing
			0.08	Tygon® tubing
			0.04	Silastic® tubing
			0.04	Silastic® tubing
			0.08 ± 0.026	Tygon® tubing. Donor dogs unfasted
			0.02±0.008	Tygon® tubing. Donor dogs unfasted
			0.16±0.032	Tygon® tubing. Donor dogs unfasted
			0.01±0.003	Tygon® tubing. Donor dogs unfasted
			0.26±0.109	Tygon® tubing. Donor dogs unfasted
			0.01±0.008	Tygon® tubing. Donor dogs unfasted
			0.007±0.0014	Tygon® tubing. Donor dogs fasted
100	108.6/hr. (C)*	0.63 (C)*	0.38	Donor dogs unfasted
100	9.14/hr. (C)*	0.053 (C)*	0.032	Steady flow
100	14.86/hr. (C)*	0.09 (C)*	0.052	Rate: 80/min. Stroke volume 25.0 ML. Donor dogs fasted
100	20.57/hr. (C)*	0.12 (C)*	0.072	Rate: 100/min. Stroke volume 20.0 ML. Donor dogs fasted
100	24.28/hr. (C)*	0.14 (C)*	0.085	Rate: 120/min. Stroke volume 16.7 ML. Donor dogs fasted
	2.5±0.18 MG./L./min.	≅0.125 (C)	≅0.075 (C)*	
200	9/hr. (E) (C)	0.035 (E)	0.005 (C)	Fasted bovine donors
400	19.28/hr. (E) (C)	0.075 (E)	0.011 (C)	Fasted bovine donors
600	90/hr. (E) (C)	0.35 (E)	0.05 (C)	Fasted bovine donors
200	9/hr. (E) (C)	0.035 (E)	0.005 (C)	Fasted bovine donors
400	12.86/hr. (E) (C)	0.05 (E)	0.007 (C)	Fasted bovine donors
600	102.86/hr. (E) (C)	0.4 (E)	0.057 (C)	Fasted bovine donors
200	12.86/hr. (E) (C)	0.05 (E)	0.007 (C)	Fasted bovine donors
400	10.28/hr. (E) (C)	0.04 (E)	0.006 (C)	Fasted bovine donors
600	77.14/hr. (E) (C)	0.3 (E)	0.043 (C)	Fasted bovine donors
200	12.86/hr. (E) (C)	0.05 (E)	0.007 (C)	Fasted bovine donors

E: Estimated from Authors' Data.
C: Calculated from Authors' Data.
*: Assuming Hematocrit of 40.
T: Total Hemoglobin (MGM.)
◦: Assuming Hematocrit of 55 to Give Lowest I.H. Using Authors' Data.

(continued)

TABLE 2
In Vitro Testing
Pulsatile Pumps—Roller Type (Cont.)

Source	Pump Description	Number of Rollers	Blood Source	Temperature	Setting	System Priming Volume (Liters)	RPM	Flow Rate (L./Min.)	Clr (I
Hahn, et al.[35] (Continued)	American Optical Co.	2	Bovine	37° C.	Partially occlusive	0.7	130 (E)	3	
	American Optical Co.	2	Bovine	37° C.	Partially occlusive	0.7	150 (E)	3	
	American Optical Co.	2	Bovine	43° C.	Partially occlusive	0.7	125 (E)	3	
	American Optical Co.	2	Bovine	43° C.	Partially occlusive	0.7	130 (E)	3	
	American Optical Co.	2	Bovine	43° C.	Partially occlusive	0.7	145 (E)	3	
	American Optical Co.	2	Bovine	10° C.	Partially occlusive	0.7	150 (E)	4**	
	American Optical Co.	2	Bovine	19° C.	Partially occlusive	0.7	145 (E)	4**	
	American Optical Co.	2	Bovine	28° C.	Partially occlusive	0.7	140 (E)	4**	
	American Optical Co.	2	Bovine	37° C.	Partially occlusive	0.7	145 (E)	4**	
	American Optical Co.	2	Bovine	43° C.	Partially occlusive	0.7	150 (E)	4**	
	American Optical Co.	2	Bovine	10° C.	Occlusive	0.7	110 (E)	3	
	American Optical Co.	2	Bovine	10° C.	Occlusive	0.7	105 (E)	3	
	American Optical Co.	2	Bovine	10° C.	Occlusive	0.7	115 (E)	3	
	American Optical Co.	2	Bovine	19° C.	Occlusive	0.7	100 (E)	3	
	American Optical Co.	2	Bovine	19° C.	Occlusive	0.7	95 (E)	3	
	American Optical Co.	2	Bovine	19° C.	Occlusive	0.7	90 (E)	3	
	American Optical Co.	2	Bovine	28° C.	Occlusive	0.7	100 (E)	3	
	American Optical Co.	2	Bovine	28° C.	Occlusive	0.7	90 (E)	3	
	American Optical Co.	2	Bovine	28° C.	Occlusive	0.7	85 (E)	3	
	American Optical Co.	2	Bovine	37° C.	Occlusive	0.7	100 (E)	3	
	American Optical Co.	2	Bovine	37° C.	Occlusive	0.7	85 (E)	3	
	American Optical Co.	2	Bovine	37° C.	Occlusive	0.7	90 (E)	3	
	American Optical Co.	2	Bovine	43° C.	Occlusive	0.7	100 (E)	3	
	American Optical Co.	2	Bovine	43° C.	Occlusive	0.7	80 (E)	3	
	American Optical Co.	2	Bovine	43° C.	Occlusive	0.7	90 (E)	3	
	American Optical Co.	2	Bovine	10° C.	Occlusive	0.7	150 (E)	4	
	American Optical Co.	2	Bovine	10° C.	Occlusive	0.7	145 (E)	4	
	American Optical Co.	2	Bovine	10° C.	Occlusive	0.7	140 (E)	4	
	American Optical Co.	2	Bovine	19° C.	Occlusive	0.7	135 (E)	4	
	American Optical Co.	2	Bovine	19° C.	Occlusive	0.7	140 (E)	4	
	American Optical Co.	2	Bovine	19° C.	Occlusive	0.7	135 (E)	4	
	American Optical Co.	2	Bovine	28° C.	Occlusive	0.7	130 (E)	4	
	American Optical Co.	2	Bovine	28° C.	Occlusive	0.7	130 (E)	4	
	American Optical Co.	2	Bovine	28° C.	Occlusive	0.7	125 (E)	4	
	American Optical Co.	2	Bovine	37° C.	Occlusive	0.7	130 (E)	4	
	American Optical Co.	2	Bovine	37° C.	Occlusive	0.7	125 (E)	4	
	American Optical Co.	2	Bovine	37° C.	Occlusive	0.7	115 (E)	4	
	American Optical Co.	2	Bovine	43° C.	Occlusive	0.7	135 (E)	4	
	American Optical Co.	2	Bovine	43° C.	Occlusive	0.7	125 (E)	4	
	American Optical Co.	2	Bovine	43° C.	Occlusive	0.7	120 (E)	4	

TABLE 2 (continued)

Pump Pressure (mm. Hg.)	Increase In Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
400	23.14/hr. (E) (C)	0.09 (E)	0.013 (C)	Fasted bovine donors
600	102.85/hr. (E) (C)	0.4 (E)	0.057 (C)	Fasted bovine donors
200	12.86/hr. (E) (C)	0.05 (E)	0.007 (C)	Fasted bovine donors
400	28.28/hr. (E) (C)	0.11 (E)	0.016 (C)	Fasted bovine donors
600	110.6/hr. (E) (C)	0.43 (E)	0.06 (C)	Fasted bovine donors
200	25.7/hr. (E) (C)	0.075 (E)	0.011 (C)	Fasted bovine donors
200	25.7/hr. (E) (C)	0.075 (E)	0.011 (C)	Fasted bovine donors
200	17.1/hr. (E) (C)	0.05 (E)	0.007 (C)	Fasted bovine donors
200	17.1/hr. (E) (C)	0.05 (E)	0.007 (C)	Fasted bovine donors
200	51.4/hr. (E) (C)	0.15 (E)	0.02 (C)	Fasted bovine donors
200	38.6/hr. (E) (C)	0.15 (E)	0.02 (C)	Fasted bovine donors
400	70.7/hr. (E) (C)	0.275 (E)	0.04 (C)	Fasted bovine donors
600	115.7/hr. (E) (C)	0.45 (E)	0.064 (C)	Fasted bovine donors
200	38.6/hr. (E) (C)	0.15 (E)	0.02 (C)	Fasted bovine donors
400	32.14/hr. (E) (C)	0.125 (E)	0.018 (C)	Fasted bovine donors
600	123.4/hr. (E) (C)	0.48 (E)	0.069 (C)	Fasted bovine donors
200	59.14/hr. (E) (C)	0.23 (E)	0.033 (C)	Fasted bovine donors
400	23.14/hr. (E) (C)	0.09 (E)	0.013 (C)	Fasted bovine donors
600	61.7/hr. (E) (C)	0.24 (E)	0.034 (C)	Fasted bovine donors
200	77.14/hr. (E) (C)	0.30 (E)	0.043 (C)	Fasted bovine donors
400	25.7/hr. (E) (C)	0.10 (E)	0.014 (C)	Fasted bovine donors
600	51.43/hr. (E) (C)	0.20 (E)	0.029 (C)	Fasted bovine donors
200	66.86/hr. (E) (C)	0.26 (E)	0.037 (C)	Fasted bovine donors
400	45/hr. (E) (C)	0.175 (E)	0.025 (C)	Fasted bovine donors
600	84.86/hr. (E) (C)	0.33 (E)	0.047 (C)	Fasted bovine donors
200	25.7/hr. (E) (C)	0.075 (E)	0.011 (C)	Fasted bovine donors
400	37.7/hr. (E) (C)	0.11 (E)	0.016 (C)	Fasted bovine donors
600	102.86/hr. (E) (C)	0.3 (E)	0.043 (C)	Fasted bovine donors
200	60/hr. (E) (C)	0.175 (E)	0.025 (C)	Fasted bovine donors
400	27.4/hr. (E) (C)	0.08 (E)	0.011 (C)	Fasted bovine donors
600	188.6/hr. (E) (C)	0.55 (E)	0.079 (C)	Fasted bovine donors
200	60/hr. (E) (C)	0.175 (E)	0.025 (C)	Fasted bovine donors
400	37.7/hr. (E) (C)	0.11 (E)	0.016 (C)	Fasted bovine donors
600	72/hr. (E) (C)	0.21 (E)	0.03 (C)	Fasted bovine donors
200	120/hr. (E) (C)	0.35 (E)	0.05 (C)	Fasted bovine donors
400	60/hr. (E) (C)	0.175 (E)	0.025 (C)	Fasted bovine donors
600	171.4/hr. (E) (C)	0.50 (E)	0.07 (C)	Fasted bovine donors
200	123.4/hr. (E) (C)	0.36 (E)	0.05 (C)	Fasted bovine donors
400	85.7/hr. (E) (C)	0.25 (E)	0.036 (C)	Fasted bovine donors
600	195.4/hr. (E) (C)	0.57 (E)	0.08 (C)	Fasted bovine donors

E = Estimated from Authors' Data.
C = Calculated from Authors' Data.
* = Assuming Hematocrit of 40.
** = Unable to Obtain Flows of 4 L./Min. Against Pressure Heads Above 200 mm. Hg With Partial Occlusion Setting Used.

TABLE 3
In Vitro Testing
Pulsatile Pumps—Finger Type

Source	Pump Description	Model or Feature	Blood Source	Temperature	Setting	System Priming Volume (Liters)	Flow Rate (L./min.)	Cir
Saltzman, et al.[36] (1949)	12 key	Elevated edged keys	Uremic human	37° C.	Nonocclusive	0.020	0.125	0
Hall, et al.[1] (1958)		Sigma T-6S	Ox	Room	Nonocclusive	0.75	1	1
		Sigma T-6S	Ox	Room	Occlusive	0.75	1	1
Leonards, et al.[20] (1958)	Sigmamotor		Canine			1.5	3	1
	Sigmamotor		Canine			1.5	3	
	Sigmamotor		Human (outdated)			2.0	3	1
McCaughan, et al.[9] (1958)	Sigmamotor	Model T-6S	Canine		Just occlusive	1.3	0.057	1
	Sigmamotor	Model T-6S	Canine		Just occlusive	1.3	0.730	1
	Sigmamotor	Model T-6S	Canine		Just occlusive	1.3	1.2	1
	Sigmamotor	Model T-6S	Canine		Just occlusive	1.3	1.75	1
Elliot, et al.[37] (1958)	Sigmamotor		Canine			0.290	1.045	1
	Sigmamotor		Canine			0.450	1.2	1
	Sigmamotor		Human			0.450	1.1	1
	Sigmamotor		Canine			0.450	1.18	1
	Sigmamotor		Human			0.450	1.3	1
	Sigmamotor		Canine			0.240	1.2	1
	Sigmamotor		Canine			0.5	1.2	1
Hodges, et al.[22] (1958)	Sigmamotor	Model TM-2	Canine		Occlusive	0.5	1.5	2
	Sigmamotor	Model TM-2	Canine		Nonocclusive	0.5	1.5	2
	Sigmamotor	Model TM-2	Canine		Occlusive	0.5	1.5	2
	Sigmamotor	Model TM-2	Canine		Nonocclusive	0.5	1.5	2
	Sigmamotor	Model TM-2	Canine		Occlusive	0.5	1.5	2
	Sigmamotor	Model TM-2	Canine		Nonocclusive	0.5	1.5	2
Björk[13] (1958)	Sigmamotor						2	
Breckler, et al.[10] (1959)	Sigmamotor		Canine			0.8	3	2
	Sigmamotor		Canine			1.0	2.4	2
	Sigmamotor		Canine			0.8	3	
Cahill, et al.[23] (1959)	Sigmamotor			25°-28.5° C.	Nonocclusive			
	Sigmamotor				Nonocclusive			
	Sigmamotor		Human		Nonocclusive	0.5-0.6	0.2-0.215	
Cappelletti, et al.[14] (1961)	Sigmamotor	Model TM-2	Canine			1.0	0.893	
	Sigmamotor	Model TM-2	Canine			1.25	2.081	
Brown, et al.[28] (1961)	Sigmamotor	Model T-6S	Human		Nonocclusive	"Small volume"	2	
Cappelletti, et al.[15] (1962)	Sigmamotor	Model TM-2	Canine			1.0	0.893	
	Sigmamotor	Model TM-2	Canine			1.25	2.081	
Martin, et al.[30] (1964)	Sigmamotor		Beef			0.52	3	
Bernstein, et al.[38] (1965)	Sigmamotor	Model TM-2					2	
Bernstein, et al.[4] (1967)	Sigmamotor	Model TM-2	Canine				1.5	
Hoffman, et al.[33] (1970)	Sigmamotor	Model TM-2	Canine			0.7		

E = Estimated from authors' data.
C = Calculated from authors' data.
* = Assuming hematocrit of 40.
† = Assuming hematocrit of 55 (from authors' data range this selected value provides lowest I.H.).

TABLE 3 (continued)

ressure Hg)	Increase in Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
20				"Faint Trace" of Hemolysis at 24 minutes
1)	40.5/hr.	0.506	0.304 (C)*	
1)	63.8/hr.	0.797	0.48 (C)*	
	83.75/hr. (E)	0.7 (E) (C)	0.42 (C)*	
	88.25/hr. (E)	0.74 (E) (C)	1.32 (C)*	#14 F. catheter restriction in line
	729/hr. (E)	8.1 (E) (C)	4.86 (C)*	
	57/hr. (E)	21.7 (E) (C)	13 (C)*	Closed system
	328/hr. (E)	9.7 (E) (C)	5.84 (C)*	Closed system
	471/hr. (E)	8.5 (E) (C)	5.1 (C)*	Closed system
	514/hr. (E)	6.4 (E) (C)	3.82 (C)*	Closed system
	163/hr. (C)	0.75 (C)	0.45 (C)*	
	355.9/hr. (C)	2.2 (C)	1.33 (C)*	
	192.1/hr. (C)	1.3 (C)	0.79 (C)*	
	305.7/1.5 hr (C)	1.3 (C)	0.78 (C)*	
	251.2/1.5 hr. (C)	0.97 (C)	0.58 (C)*	
	336.1/1.5 hr. (C)	0.75 (C)	0.45 (C)*	
	108.9/1.5 hr. (C)	0.5 (C)	0.30 (C)*	
	285/2 hrs.	0.8 (C)	0.475 (C)*	Stroke volume 17 CC., #14 F. catheter, ¼ inch I.D. tubing.
	199/2 hrs.	0.55 (C)	0.33 (C)*	Stroke volume 17 CC., #14 F. catheter, ¼ inch I.D. tubing.
	103/2 hrs.	0.29 (C)	0.17 (C)*	Stroke volume 40 CC., #14 F. catheter, ¼ inch I.D. tubing.
	131/2 hrs.	0.37 (C)	0.22 (C)*	Stroke volume 40 CC., #14 F. catheter, ¼ inch I.D. tubing.
	93/2 hrs.	0.26 (C)	0.16 (C)*	Stroke volume 40 CC., #16 F. catheter, ⅜ inch I.D. tubing.
	72/2 hrs.	0.2 (C)	0.10 (C)*	Stroke volume 40 CC., #16 F. catheter, ⅜ inch I.D. tubing.
		2.25 (C)		
	144/2 hrs.	0.32 (C)	0.320	No line constriction
	384/2 hrs.	1.3 (C)	1.334	0.25 inch I.D. cannula restriction in line
	102/hr.	0.45 (C)	0.453	Pulse rate 125 cycles/minute
	19/hr.			
	20/hr.			
0	11.6/hr.	0.45-0.58 (C)	≅ 0.27-0.35 (C)*	Rate of accumulation of free hemoglobin increased to 20 MGM./100 ML./hr. when run for 16 hours
	86.7/hr.	1.6 (C)	2.0	Recalculated I.H.: 0.97 (C)*
	97.8/hr.	0.98 (C)	1.02	Recalculated I.H.: 0.59 (C)*
lood	0.333 MG./L./hr.		0.033	
	86.7/hr.	1.6 (C)	1.62	Recalculated I.H.: 0.97 (C)*
	97.8/hr.	0.98 (C)	0.980	Recalculated I.H.: 0.59 (C)*
	1592/2.88 hrs.	1.592	0.72 (C)†	
			0.60	
			0.60	
			0.95	

TABLE 4
In Vitro Testing
Pulsatile Pumps—Ventricle Type

Source	Pump Description	Pump Activation	Blood Source	Temperature	Chamber Volume	System Priming Volume (Liters)	Rate (Cycles per minute)	Stroke Volume (CC.)	Flow Rate (L./min.)
Björk[39] (1948)	Crafoord pump	Pneumatic	Canine	37° C					
Rotellar[40] (1958)	Three chambered	Pneumatic			160 CC.	0.3		15	0.2
Röckemann[41] (1958)	Single chamber	Pneumatic	Bovine			0.350	60		
Elliot, et al.[37] (1958)	Nonocclusive compression	Cam driven	Canine	Room	250 CC.	0.5			0.850
			Canine			0.45			1.2
			Human			0.45			1.2
			Canine			0.49			1.2
			Human			0.45			1.3
			Canine			0.375			1.2
			Canine			0.545			1.2
Hufnagel, et al.[42] (1958)	Dual sac	Pneumatic			75 CC.				
Breckler, et al.[10] (1959)	UPI pump (nonocclusive compression)	Hydraulic	Canine		87 CC. (C)	0.8			3.0
					87 CC. (C)	1.0			2.4
					87 CC. (C)	0.8	80		1.5
					87 CC. (C)	0.8	60		3.0
					87 CC. (C)	0.8	80		3.0
					87 CC. (C)	0.8	100		3.0
					87 CC. (C)	0.8	80		4.5
Cahill, et al.[23] (1959)	MacNeill-Collins pump	Hydraulic	Human	25°-28.5° C.		0.5-0.6	28-32		0.2-0.2
Sorensen, et al.[43] (1960)	Nonocclusive compression	Hydraulic		37° C.		1			6
Barila, et al.[44] (1962)	Army artificial heart pump	Pneumatic							2
Nunn, et al.[45] (1963)	Army heart pump	Pneumatic	Human						
Martin, et al.[30] (1964)	Davol	Pneumatic	Beef			0.6			3.0
Castañeda, et al.[46] (1964)	Army heart pump	Pneumatic	Canine						1.5 2.0 3.5
Kusserow, et al.[47,32] (1964) (1965)	Fluid filled hydraulic chamber	Cam driven	Canine			0.5			1.225
Bernstein, et al.[4] (1967)		Mechanical cam driven	Canine						
	Dorman silastic ventricle.		Canine						
	Army heart pump.		Canine						
	Bluemle triple ventricle.		Canine						
Nakamura, et al.[48] (1969)	Sac	Hydraulic	Canine						
	Sac	Hydraulic	Canine						
Klain, et al.[34] (1970)	Conventional sac	Pneumatic	Cow			70-130 (R) 75-130 (L)	2.5		55-110 (R) 60-112 (L)
	Wave-pulsating total heart	Pneumatic	Cow			134 (R) 154 (L)	2.5		112 (R) 134 (L)
Smith, et al.[49] (1974)	Various configurations	Pneumatic							

C = Calculated from Authors' Data.
* = Assuming hematocrit of 40.
†=Test period graphically depicted as 4 hours although times of various experiments reported to be 16-31 hours.

TABLE 4 (continued)

ation ne rs)	Pump Pressure (mm. Hg)	Increase in Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
		160/3 hrs.			
					No hemolysis
	120	7/1.5 hrs. (serum)			0.05% hemolysis
		12.2/hr.	0.12 (C)	0.07 (C)*	
		32.2/hr.	0.2 (C)	0.12 (C)*	
		47.3/hr.	0.3 (C)	0.18 (C)*	
		30.9/1.5 hrs.	0.14 (C)	0.08 (C)*	
		27.3/1.5 hrs.	0.1 (C)	0.06 (C)*	
		72.0/1.5 hrs.	0.25 (C)	0.15 (C)*	
		24.0/1.5 hrs.	0.12 (C)	0.07 (C)*	
		10/hr.			Silicone rubber ventricle
		31/2 hrs.	0.07 (C)	0.069	No line constriction
		14/2 hrs.	0.05 (C)	0.043	Recalculated I.H.: 0.049. ¼ inch line constriction.
		13/hr.	0.12 (C)	0.116	No line constriction
		13/hr.	0.06 (C)	0.058	No line constriction
		13/hr.	0.06 (C)	0.058	No line constriction
		12/hr.	0.05 (C)	0.053	No line constriction
		18/hr.	0.05 (C)	0.053	No line constriction
	80/50	15-17/hr.	$\cong$0.145-21 (C)	$\cong$0.35-0.51 (C)*	
		$<$4/30 min.	$<$0.02 (C)	$\cong<$0.013 (C)*	Bank Blood
		0.31/30 min.			Polyvinyl chloride ventricle
		14.3265$\pm$1.6523/ 37.5 min.			No significant difference in using various valves
/3	100	205 per 3 1/3 hrs.*	0.205	$\cong$0.09-0.11 (C)	
	140 CM. blood			0.08	Polypropylene butterfly valves and rubber ventricles
	140 CM. blood			0.18	Polypropylene butterfly valves and rubber ventricles
	140 CM. blood			0.09	Polypropylene butterfly valves and rubber ventricles
		0.33/hr. (C)*	0.0022 (C)*	0.08	Individual indices of hemolysis as low as 0.059 were obtained
				0.82	
				0.13	
				0.09	
				0.09	
		11/4 hrs.			
		5/4 hrs.			
		14.4-29.6/5 hrs.	0.024-0.044 (C)	0.01-0.03 (C)*	
		13.7-26.3/5 hrs.	0.023-0.044 (C)	0.01-0.03 (C)*	
				0.04	

TABLE 5
In Vitro Testing
Pulsatile Pumps—Diaphragm Type

Source	Pump Description	Pump Activation	Blood Source	Temperature	Chamber Volume	System Priming Volume (Liters)	Rate (Cycles Per Minute)	Stroke Volume (CC.)	Flow Ra (L./Min
Dennis, et al.[18] (1951)	Modified Dale-Schuster	Through fluid medium with rubber bellows.				0.5	24		1.5
	Modified Dale-Schuster	Through fluid medium with rubber bellows.				0.5	24		.953
Dodrill, et al.[50] (1952)	Modified Dale-Schuster	Pneumatic							
Field, et al.[51] (1958)	Dual pumping chambers	Hydraulic Piston	Human			0.020		0.68	0.001
			Rat			0.020		0.68	0.001
			Rabbit			0.020		0.68	0.001
			Human			0.020		0.68	0.003
			Rat			0.020		0.68	0.003
			Rabbit			0.020		0.68	0.003
			Human			0.020		0.68	0.006
			Rat			0.020		0.68	0.006
			Rabbit			0.020		0.68	0.006
Cahill, et al.[23] (1959)	Dale-Schuster (modified Olson model).		Human	25°-28.5° C.		0.5-0.6	28-32		0.2-0.2
	Dale-Schuster (Sindelar modification)		Human	25°-28.5° C.		0.5-0.6	28-32		0.2-0.2
	Dale-Schuster (modified Olson model).		Human	25°-28.5° C.		0.5-0.6	28-32		0.2-0.2
Cappelletti, et al.[14] (1961)	Modified Dale-Schuster		Canine			1			0.86(
	Modified Dale-Schuster		Canine			1.250			1.91:
Fry, et al.[52] (1961)	Two-chambered device	Eccentric drive from synchronous motor				0.5			1.5
Brown, et al.[28] (1961)	Foregger pulspirator	Mechanical pneumatic.	Human			"Small volume"			2
Hastings, et al.[53,54] (1961) (1962)	Dual chamber Modified Dale-Schuster	Hydraulic							0.25
	Dual chamber Modified Dale-Schuster	Hydraulic							3.5
Cappelletti, et al.[15] (1962)	Modified Dale-Schuster		Canine			1			0.86
	Modified Dale-Schuster		Canine			1.250			1.91
Clark, et al.[55] (1971)	Harvard pulsatile blood pump and remote head assembly	Hydraulic	Human		12 CC.	0.5			1
Ross, et al.[56] (1972)	Baylor-Rice total orthotopic cardiac prosthesis	Pneumatic							

C = Calculated from authors' data.
* = Assuming hematocrit of 40.
Δ = Calculated on basis of one hour circulation time. Because of small priming volume, after first sample drawn the priming volume was significantly affected.

TABLE 5 (continued)

ulation ime ours)	Pump Pressure (mm. Hg)	Increase in Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
2/3	0	44//2/3 hr.	0.367 (C)	0.365	Recalculated I.H.: 0.22 (C)*
3/4	100	26//3/4 hr.	0.303 (C)	0.303	Recalculated I.H.: 0.182 (C)*
					No significant hemolysis
		5.0 (at 1 hour)	1.67 (C)	1.0 (C)*Δ	
		5.0 (at 1 hour)	1.67 (C)	1.0 (C)*Δ	
		1.8 (at 1 hour)	0.6 (C)	0.36 (C)*Δ	
		4.2 (from 1st-2nd hour)	0.47 (C)	0.21 (C)*Δ	
		2.5 (at 1 hour)	0.28 (C)	0.17 (C)*Δ	
		1.8 (at 1 hour)	0.2 (C)	0.12 (C)*Δ	
		8.3 (at 1 hour)	0.46 (C)	0.28 (C)*Δ	
		3.1 (at 1 hour)	0.17 (C)	0.10 (C)*Δ	
		3.5 (at 1 hour)	0.19 (C)	0.12 (C)*Δ	
	80/50	3.5/hr.	0.136-0.175 (C)	≅0.08-0.1 (C)*	
	80/50	1.4/hr.	0.05-0.07 (C)	≅0.03-0.04 (C)*	
	80/50	2.5/hr.	0.097-0.125 (C)	≅0.05-0.08 (C)*	
	120	40.7/hr.	0.788 (C)	1.14	Recalculated I.H.: 0.47 (C)*
	120	99.8/hr.	1.087 (C)	0.93	Recalculated I.H.: 0.65 (C)*
		30/hr.	0.17 (C)	0.1 (C)*	Canine and human blood used. Peripheral and pulmonary circulations differ in phase by one-half cycle.
	140 CM. blood	0.0266/30 min.		0.027	
		3.7/hr.			
		40/hr.			
	120	40.7/hr.	0.788 (C)	0.788	Recalculated I.H.: 0.47 (C)*
	120	99.8/hr.	1.087 (C)	1.085	Recalculated I.H.: 0.65 (C)*
		0.59/min.	0.295 (C)	0.18 (C)*	
	"Physiologic"			<0.08 (C)	"<0.8 MG. plasma hemoglobin are formed per liter of blood pumped."

TABLE 6
In Vitro Testing
Pulsatile Pumps—Piston Type

Source	Pump Description	Pump Activation	Blood Source	Temperature	Chamber Volume	System Priming Volume (Liters)	Rate (Cycles Per Minute)	Stroke Volum (CC.)
Brodie[57] (1903)	Single piston. Blood contacting surface of glass, rubber tubing, wood, and leather							
Hall, et al.[1] (1958)	Candy Major GMV/SS.28G.		Ox	Room		0.75		
	Candy Minor MM/SS.30G.		Ox	Room		0.75		
	Candy Major		Ox	Room		0.75		
	Girdlestone DMF 100		Ox	Room		0.75		
Bluemle[58,59] (1958)	Double piston, low output pump. Blood pumped by 2 syringes via air cushion	Motor driven syringes						
Brown, et al.[28,60] (1961)	Seidel-Curtis Bellofram.		Human				28	
	Seidel-Curtis Bellofram.		Human				28	
	Seidel-Curtis Bellofram.		Human					
	Seidel-Curtis Bellofram.		Canine					
	Bellofram artificial heart.	Pneumatic	Human				108	28
Smith, et al.[49] (1974)	Soft shell	Scotch yoke					120	111

C =Calculated from authors' data.
* = Assuming hematocrit of 40.

TABLE 7
In Vitro Testing
Pulsatile Pumps—Bar Compression Type

Source	Pump Description	Pump Activation	Blood Source	Temperature	Chamber Volume	System Priming Volum (Liters)
Björk[13] (1958)	Crafoord-Senning-AGA	Two parallel pumps working alternately				
Poth[61] (1958)	Poth	Piston				
Senning[62] (1958)	Sabbatsbergs Hospital machine		Human			
Akutsu, et al.[26] (1960)	Pendulum		Human		2 mm. x 25 mm.	
Houston, et al.[63] (1960)	Pendulum	General Electric motor (D.C.)	Human			
	Pendulum	General Electric motor (D.C.)	Human			
	Pendulum	Globe motor (AC)	Human	Room		
	Pendulum	Globe motor (AC)	Human	Room		
Brown, et al.[28] (1961)	Pendulum		Human			"Small volume"

C = Calculated from author's data.
A = Authors' estimate.

TABLE 6 (continued)

Flow Rate (L./Min.)	Circulation Time (Hours)	Pump Pressure (mm. Hg)	Increase In Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
						Red corpuscles "suffer to a slight degree."
1	1	100	12.4/hr.	0.155	0.093 (C)*	80 circuits
1	1	100	16.2/hr.	0.202	0.122 (C)*	80 circuits
5	1	100	53.7/hr.	0.134	0.08 (C)*	400 circuits
3.8	1	100	79.8/hr.	0.525	0.158 (C)*	152 circuits
						". . . no hemolysis that we can measure." Flow capacity 0-0.5 L./min.
2		140 CM. blood	7.5/hr. (C)		0.0197	3-cusp semilunar polyurethane valves.
2		140 CM. blood	30/hr. (C)		0.028	Thicker semilunar valves
2		140 CM. blood	7.5/hr. (C)		0.008	Flat rubber valves
2		140 CM. blood			0.003	
2		140 CM. blood	15/hr. (C)		0.011	
12		100			0.008	Alternating 2 chamber pumping

TABLE 7 (continued)

ow Rate -/Min.)	Circulation Time (Hours)	Pump Pressure	Increase In Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
			222//1 2/3 hrs. (C)	2.2 (C)		100 passages through pump
/3	0.5		0.67/0.5 hr.			
				0.5		
	3		30/hr.			Systemic circuit
	3		15/hr.			Pulmonary circuit
	3		30/hr.			Systemic circuit
	3		15/hr.			Pulmonary circuit
5	2	100 CM. blood	25/hr.			Systemic circuit
5 (A)	2	25 CM. blood	12/hr.			Pulmonary circuit
	2	140 CM. blood	0.0366/30 min.		0.037	

TABLE 8
In Vitro Testing
Nonpulsatile Pumps

Source	Pump Description	Pump Type	Blood Source	Temperature	System Priming Volume (Liters)	RPM	
Hall, et al.[1] (1958)	Norman Blackmer "D" pump	Impellor	Ox	Room	0.75		1
	Mono SB 15R5/B	Screw	Ox	Room	0.75		1
	Stewart Turner pump No. 10	Centrifugal	Ox	Room	0.75		10
	Mono	Screw	Ox	Room	0.75		5
Hall, et al.[64] (1959)	Modified Mono	Screw	Ox				
Saxton, et al[2] (1960)	Commercial 2 inch diameter, polyethylene head and impeller	Centrifugal					
Brown, et al.[28] (1961)	Donaldson Mono	Screw	Human				2
Bernstein, et al.[4] (1967)	Ormonde-Mono	Screw	Canine				2
Dorman, et al.[65] (1969)	Centrifugal	Shear impeller	Calf			1750	1
	Centrifugal	Shrouded impeller	Calf			1200	5
	Centrifugal	Turo	Calf			800	2
	Centrifugal	Turo	Calf			1500	4
	Centrifugal	Turo	Calf			1600	5
	Centrifugal	Velocity head (4 blade)	Calf			4000	6
	Centrifugal	Velocity head (6 blade)	Calf			3820	6
Bernstein, et al.[66] (1974)	Centrifugal	Mark II	Calf	Room		4000	
	Centrifugal	Mark IV	Calf	Room		4000	
	Centrifugal	Rotating impeller	Calf	Room	>0.521 (C)	6000	
	Centrifugal	Rotating impeller	Calf	Room	>0.521 (C)	7000	
	Centrifugal	Rotating impeller	Calf	Room	>0.521 (C)	8000	
	Centrifugal	Rotating impeller	Calf	Ice water	>0.521 (C)	7000	
	Centrifugal	Rotating impeller	Calf	Ice water	>0.521 (C)	8000	
	Centrifugal	Rotating impeller	Calf	Room	>0.521 (C)	6000	
	Centrifugal	Rotating impeller	Calf	Room	>0.521 (C)	7000	
	Centrifugal	Rotating impeller	Calf	Room	>0.521 (C)	8000	
Kletschka, et al.[67] (1975)	Constrained force-vortex	Model 100 Series	Horse	37° C.	5	1500-2500	11
	Constrained force-vortex	Model 100 Series	Horse-prelysed	37° C.	5.5	1500-2500	11
	Constrained force-vortex	Model 200 Series	Horse-prelysed	37° C.	5.5	1500-2500	9
	Constrained force-vortex	Model 200 Series	Horse-prelysed	37° C.	5.5	1500-2500	9
	Constrained force-vortex	Model 200 Series	Horse	37° C.	5.5	1000-2500	6
	Constrained force-vortex	Model 200 Series	Horse	37° C.	5.14	2000	6
	Constrained force-vortex	Model 200 Series	Horse	37° C.	4.73	1000-2500	5
	Constrained force-vortex	Model 200 Series	Horse	37° C.	4.56	1500-2500	7
	Constrained force-vortex	Model 200 Series	Horse	37° C.	4.61	500-1400	8
	Constrained force-vortex	Model 200 Series	Horse	37° C.	4.27	1500-2500	9
	Constrained force-vortex	Model 200 Series	Horse	37° C.	4.62	3000-3500	3
	Constrained force-vortex	Model 200 Series	Horse	37° C.	3.805	1000-1500	6

C = Calculated from authors' data.
* = Assuming hematocrit of 40.
□ = Mean values.

TABLE 8 (continued)

ulation ime ours)	Total Flow (Liters)	Pump Pressure (mm. Hg)	Increase In Plasma HGB. (MGM. %) Per Unit Time	Hemolysis Per Passage (MGM. % Plasma HGB.)	Index of Hemolysis	Comments
	60 (C)	100	69.3/hr.	0.866	0.52 (C)*	
	60 (C)	100	29.5/hr.	0.370	0.22 (C)*	
	600 (C)	100	1333.5/hr.	1.666	1.00 (C)*	
(C)	300 (C)	100	171.4/hr.	0.428	0.26 (C)*	
						Has hemolysis rate similar to that of the industrial model
						5% drop in hematocrit first hour and 1% per hour thereafter
		140 CM. Blood	4.8/L./30 min.		0.480	
					2.69	
		90			0.66	
		57			0.13	
		15			0.021	
		55			0.082	
		62			0.086	
		100			0.016	
		100			0.005	
		100			0.005	
		100			0.010	
		100			0.004	
		100			0.043	
		100			0.111	
		100			0.003	
		100			0.012	
		100			0.006	Rotor infusion @ 0.4 ML./min.
		100			0.021	Rotor infusion @ 0.4 ML./min.
		100			0.120	Rotor infusion @ 0.4 ML./min.
/60	1737.15	20-62.5	0.000	0.000	0.000	Company pump reference No. CS−6.35NcT3HYTDEE72
/60	2784	20-62.5	0.000	0.000	0.000	Company pump reference No. CS−6.35NcT3HYTDEE72
/60	1167	53-61	0.000	0.000	0.000	Company pump reference No. MmS−6.35NcT3HYTMEE73
/60	1189.2	53-61	0.000	0.000	0.000	Company pump reference No. MmA−6.35NcT3HYTMEE73
5/60	3607.1	49-61	0.000	0.000	0.000	Company pump reference No. MmA−6.35NcT3HYTMEE73
/60	420	105	0.000	0.000	0.000	Company pump reference No. MmS+6.35NcT3SYTMEE73
0	2743	53-70	0.000	0.000	0.000	Company pump reference No. MmS+6.35NcT3SYTMEE73
/60	3318.4	61-89	0.000	0.000	0.000	Company pump reference No. MmS+6.35NcT3SYTM-EE74
/60	3933	45-103	0.000	0.000	0.000	Company pump reference No. MmS−12.7NcT3SYTMEE74
0	27849	53-89	0.235/hr.□	0.0018□	0.001	Company pump reference No. MmS+6.35NcT3SYTM-EE74
0	227	180-198	0.000	0.000	0.000	Company pump reference No. MmS+6.35NcT3SYTcM-EE74
5/60	3694.1	30-70	0.000	0.000	0.000	Company pump reference No. MmS+7.87NcT3SYTM-EE75

pumps from the standpoint of being able to circulate blood atraumatically. For example, the rolling diaphragm piston pump, which has recently found application as an artificial heart pump,[49] has exhibited gentler blood handling capabilities. Undoubtedly, the wide acceptance of the roller pump is, therefore, related to other factors than its less than optimum blood handling characteristics.

Centrifugal Pumps

The centrifugal pump was originally felt to be the most destructive type pump in circulating fluids. However, a review of Tables 1 and 8 shows that through application of proper design ingenuity, these pumps have now been developed by our group to the point where they are the most atraumatic of all blood pumps. It is anticipated, therefore, that the *constrained force-vortex pump* described herein should find extended application in the future for all situations involving circulation of blood.

Advantages of Constrained Force-Vortex Pump

Such pumps are efficient; and, because they utilize only one moving part, are very reliable and durable. Problems currently associated with the use of conventional roller pumps such as splitting of tubing, disruption with inadvertent occlusion of tubes, and spallation of foreign particulate matter into the blood stream by the squeezing and erosive action of the rollers on the tubing will be obviated in using the BIO-MEDICUS Rafferty/Kletschka blood pump. We feel spalled plastic particles are undoubtedly responsible for much of the heart (e.g., subendocardial necrosis and "stone heart" syndrome), brain, and other organ damage observed in patients following conventional open-heart surgery.

Hemolysis

Testing for hemolysis by a blood pump under in vitro conditions is a severe test by any standard.[23,28] Björk has stated that mechanical hemolysis in a perfusion apparatus is impossible to avoid.[39] However, it is apparent, on reviewing the Tables, that the various pumps have not all been tested under similar in vitro conditions. Nevertheless, calculating the index of hemolysis and the hemolysis per passage for each pump, does permit a meaningful evaluation of each pump for the conditions under which it was tested. Although some pumps exhibit acceptably low indices of hemolysis, such results have been almost universally achieved under artificially favorable conditions as they relate to blood source, temperature, flow rates, circulation times, and pump pressures.

The osmotic fragility of horse and ox blood is greater than that of canine blood which, in turn, is greater than that of human blood.[70,71] We, therefore, elected to use horse blood in our experiments to render the conditions of our test program more critical. In addition, large volumes of blood can be frequently and repeatedly obtained from a single horse as a donor source, making comparisons between tests of one pump model against another more valid. Further, problems relating to incompatibilities among donors using pooled blood are avoided. To further increase the critical conditions under which our pump was tested, we used pre-lysed horse blood in certain experiments. The purpose of using pre-lysed horse blood was to create a population of erythrocytes of varying degrees of susceptibility to damage by a given destructive force. Under these conditions, a certain percentage of the red blood cell population in a given volume of blood should be subject to lysis by the application of only a minimal amount of destructive force. In other words, using pre-lysed blood theoretically should create a situation in which the application of only a very small destructive force to the blood should be reflected in an elevation of plasma hemoglobin values.

Fragility vs. Temperature

All of our tests were carried out at 37° C. It has been observed that blood is more fragile at body temperature than at room temperature.[4,18,72,73] Inasmuch as the operating environment of an artificial heart will be at body temperature, it is important that blood testing, using the pump component of such a prosthesis, be carried out at 37° C.

Effect of Flow Rate and Time

Some blood pumps reported on in the literature were tested at flow rates as low as 0.001 L./min, and none were recorded which were tested at the very high flow rates we used in our experiments. In some of our tests flow rates up to 25 L./min were used, clearly above the range of normal physiological requirements by several fold. Calculations by one of our group (D.A.O.) have shown that at such high blood flow rates, turbulence in the blood flowing through the tubing can occur unless impracticably large diameter flow conduits are used. Any hemolysis, therefore, occurring at such high flow rates could be due to

turbulence caused by the excessive velocity of blood within the tubing rather than to destructive effects of the pump per se.

Most in vitro pumping experiments in which hemolysis occurs demonstrate that a linear increase takes place with time if other factors are kept constant.[1,14-16,19,23,28,39,54,63] Perhaps, because unrefrigerated blood, particularly at body temperature, undergoes autolysis with time,[4,73] few in vitro hemolysis testing experiments have been reported which have extended beyond a few hours. Our experiments incorporated tests in which blood was circulated for periods of over 48 hours. There is probably little need in routine in vitro blood pump testing to carry out circulation for such long periods since delayed destruction of erythrocytes has been shown to be directly related to acute injury, anyway.[4,73]

Head of Pressure

Application of blood pumps for ex vivo or in vivo use will, in most instances, require that the unit can perform satisfactorily against a normal head of pressure. Our blood pump testing program included tests in which pump pressures of approximately twice physiological mean levels were achieved.

It is evident, from a review of the reported blood pumps, that none has been tested under the extremely rigorous and supercritical conditions to which the Rafferty/Kletschka Blood Pump (Bio-Pump®†) has been subjected. Yet, even under these rigid test conditions, our blood pump has been shown to be more atraumatic than any of the other reported pumps.

Criteria have been established to define blood handling requirements for a blood pump intended for use as the pumping unit of an artificial heart. Bernstein, et al.[4,38] have reported that the rate of red blood cell destruction in an adult man yields a normal index of hemolysis of approximately 0.05. His group felt a 70 kilogram man might tolerate indefinitely an index of hemolysis of 0.1 if provided supplemental iron. These figures delineate goals for minimally acceptable blood handling qualities of a prospective artificial heart blood pump. When tested in vitro, the capability of a blood pump to operate within the prescribed tolerable limits must be demonstrated in experiments embracing those conditions under which the natural heart functions.

†Registered trademark, Bio-Medicus, Inc.



Figure 1—BIO-MEDICUS Rafferty/Kletschka artificial heart pump.



Figure 2—BIO-MEDICUS Rafferty/Kletschka blood pump for extracorporeal applications.

Atraumatic Characteristics

The atraumatic characteristics of our blood pump render it immediately attractive, not only as an artificial heart pump (Figure 1) but also as the pump component for a heart-lung machine (Figure 2).

With the development of our efficient atraumatic blood pump, we feel the most formidable barrier to the successful attainment of an artificial heart has been overcome. The design features of a nonpulsatile pump such as the BIO-MEDICUS Rafferty/Kletschka Blood Pump permit a wide selection of materials from which compatible

biological surfaces may be fashioned. Zero hemolysis has been achieved in the experiments reported using Pyrolite® carbon and polymethylmethacrylate for the surfaces exposed to blood.

Autoregulatory

The inherent autoregulatory nature of a centrifugal pump such as ours minimizes the need for appurtenant regulatory devices. Short term in vivo and ex vivo testing, which we have carried out, suggests that in certain instances no regulatory capability will have to be added to the system beyond that possessed by the pump itself.

Because the unit exhibits a high pump efficiency, great flexibility should be enjoyed in adapting it to a suitable compact power source. It is envisioned that the best of any suitable power source, selected from among the many being developed, can be satisfactorily interfaced with the pump. Regardless of the mode in which the reported pump is selected to operate, reliability is encouraged by the fact it contains only one moving part.

The blood pump has been used as the pumping component of a heart-lung machine system in which dogs have been sustained for over three hours of total body perfusion with recovery and with no ill effects noted over periods of long term observation. Clinical application of the unit appears warranted.*

*N.B. Since submittance of this manuscript the first clinical application of the constrained force-vortex pump was carried out on July 16, 1975. The patient, Miss Barbara G. Kletschka, successfully underwent a short-term veno-venous perfusion, autotransfusion, and assist with the unit.

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Farrell Stiegler, M.D.
Cover Editor

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(Continued on page 786)

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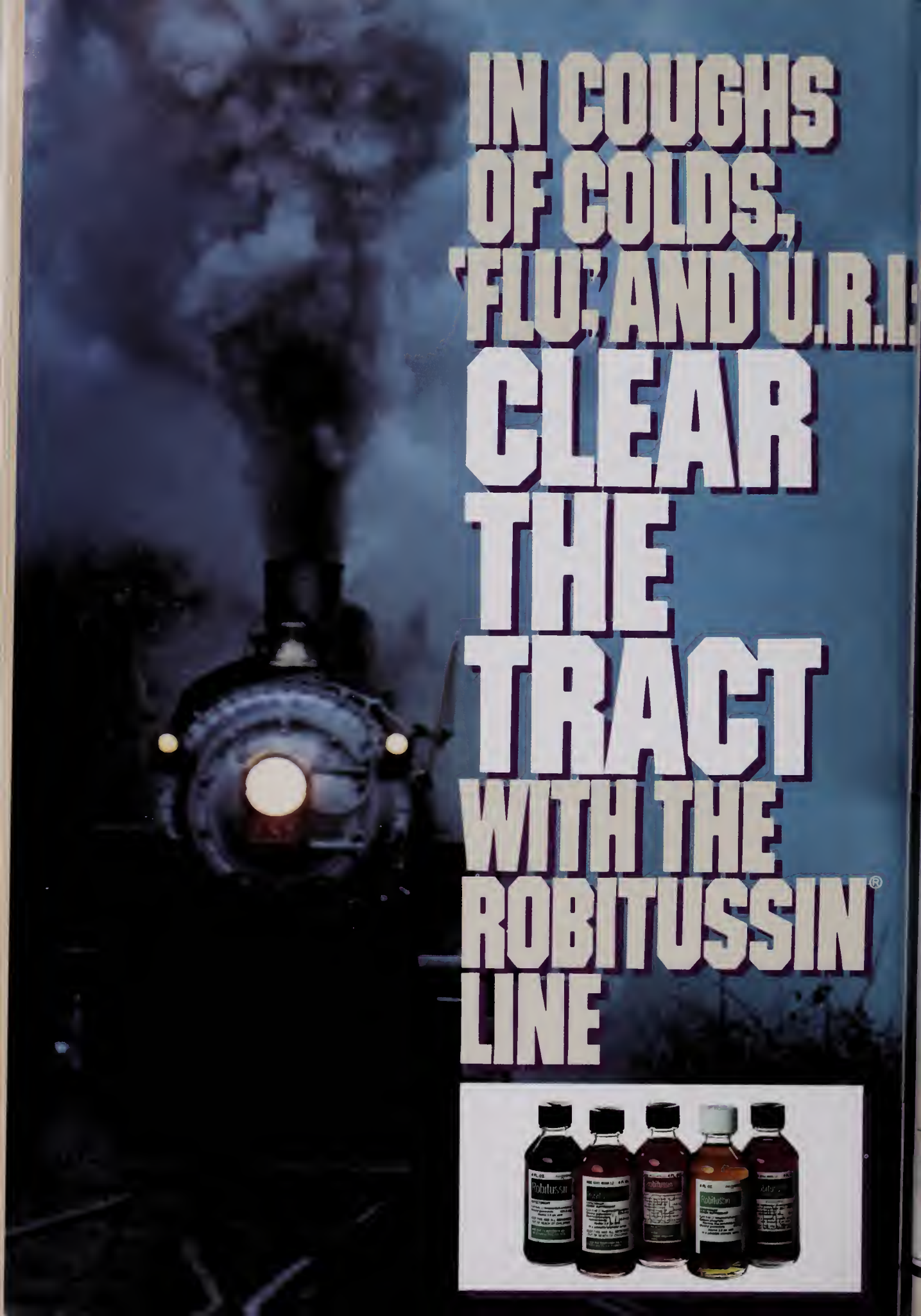
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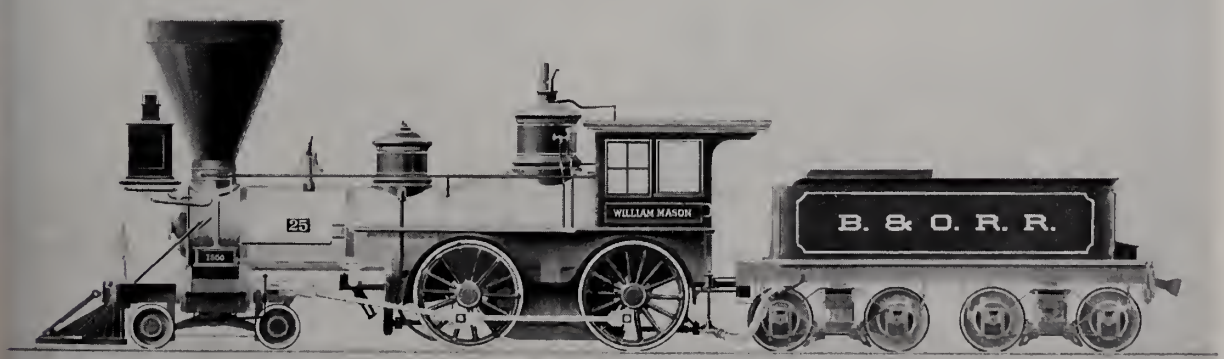
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The William Mason (1856)

(Continued from page 782)

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(Continued on page 794)

Fracture Conference

Traumatic Peroneal Tendinitis
A Complication of Calcaneal Fractures

ROBERT H. FITZGERALD, JR., M.D.,* R. MICHAEL GROSS, M.D.† and KENNETH A. JOHNSON, M.D.*

Dr. Robert H. Fitzgerald, Jr.:

Calcaneal fractures are associated with a significant morbidity and a prolonged period of unemployment. Although experienced orthopedic surgeons have studied their results and advocated different methods of treatment,[1-4] the pessimistic attitude expressed by Bankart[5] 30 years ago remains associated with calcaneal fractures. Our discussion concerns one possible cause for pain and its treatment after healing of a calcaneal fracture.

Case 1

The first patient to be discussed is a 21-year-old man who came to the emergency room after falling 66 feet from a silo. He complained of pain in both heels but related that he had not lost consciousness. Other than the bilateral foot pain, he felt well. On examination, he had a full range of motion of the left ankle and subtalar joint with some mild tenderness over the heel pad. The right heel was swollen, exquisitely tender, and painful with motion of the subtalar or ankle joint. X-ray examination was performed (Figures 1 and 2).

Dr. Cooney, would you describe what you see on these roentgenograms?

Dr. William P. Cooney III:

There is evidence of a linear fracture through the body of the calcaneus with a fracture line extending into the subtalar joint.

Dr. Fitzgerald:

Dr. Cooney, are there any other x-ray examinations that you would require for evaluation of this patient in the emergency room?

Dr. Cooney:

Yes, I would want anteroposterior and lateral x-ray views of the patient's lumbosacral spine.

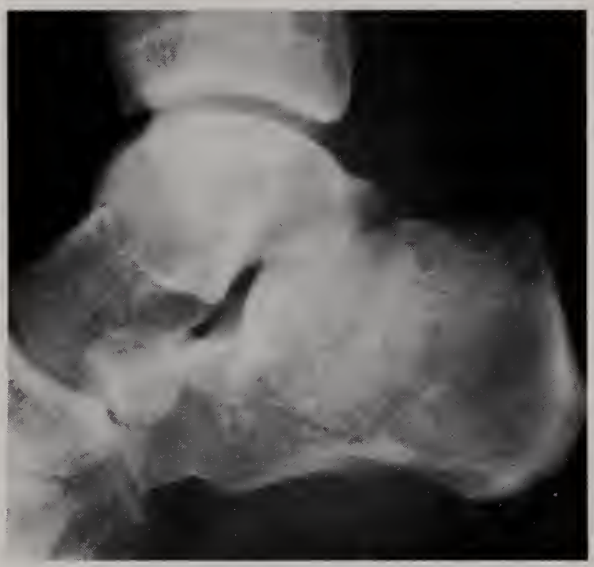


Fig. 1—Joint depression type of fracture of os calcis.[2]



Fig. 2—Anteroposterior view of ankle demonstrating lateral displacement of lateral cortex of calcaneus at level of subtalar joint.

*Consultant, Department of Orthopedics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
†Resident in Orthopedics, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.
Address reprint requests to Dr. R. H. Fitzgerald, Mayo Clinic, Rochester, Minnesota 55901.

Dr. Fitzgerald:

Clinical examination showed the patient's back to be normal. On x-ray examination, there was no evidence of fracture. Dr. Cooney, how would you manage this fracture if you had seen this patient in the emergency room?

Dr. Cooney:

I would have used a Robert Jones dressing and elevation of the extremity until the swelling was down. Then I would have applied a non-weight-bearing cast.

Dr. Fitzgerald:

This patient was treated as Dr. Cooney suggested. Eight weeks after the fracture, roentgenograms revealed evidence of early callous formation. The patient was instructed to begin range-of-motion exercises and crutch walking with only touch down of the foot. Eleven weeks after the injury, he began weight bearing as tolerated by pain. About 13 weeks after sustaining the calcaneal fracture, the patient presented with pain over the lateral aspect of his left ankle. He was thought to have peroneal tendinitis and was given an injection of betamethasone (Celestone). After this treatment, he did well until February 1974. At that time, he returned complaining of pain over the lateral aspect of his ankle. He related that pain over the lateral aspect of his ankle prevented walking without shoes. Wearing high-top boots, the patient was able to walk approximately 300 feet on level ground before he experienced pain over the lateral aspect of his ankle and foot. Walking over uneven ground precipitated pain after a few steps.

Examination revealed localization of the patient's discomfort over the peroneal tendons at the level of the subtalar joint. The tendon sheaths of the peroneal tendons were injected with 2 ml of 1% lidocaine (Xylocaine). Immediately after the injection, the patient experienced complete relief of pain and was able to walk as far as he wished.

We felt that the exostosis over the lateral aspect of the subtalar joint and adhesions within the tendon sheath were etiologic factors precipitating peroneal tendinitis. A tenogram was made (Figure 3). We could easily inject the dye into the sheath of the peroneal tendons and visualize the sheath to the level of the subtalar joint. When attempting to inject the sheath distal to this level, the patient experienced discomfort. With further pressure, however, we were able to inject the entire sheath. The tenogram demonstrated narrowing and incomplete filling of the peroneal tendon sheaths distal to the level of the subtalar joint.



Fig. 3—Incomplete filling of peroneal tendon sheath is noted just proximal to level of subtalar joint on anteroposterior view (A) and lateral view (B).

We advised surgical decompression of the tendon sheath and the removal of the exostosis about the lateral aspect of the subtalar joint as described by Kashiwagi and Inamatsu.[6] At the time of operation, the peroneal tendons were completely scarred along the lateral aspect of the calcaneus at the level of the subtalar joint. Once the adhesions were removed, the tendons were noted to move freely within their sheath. The tendons, however, were riding over a rough bone spike on the lateral wall of the calcaneus. The tendon sheaths were dissected free of this area and the heterotopic bone was excised. The retinaculum at the fibula was repaired. The tendon sheaths were left open and the subcutaneous tissues and skin were closed in a routine fashion. Immobilization for three weeks was prescribed, to be followed by range-of-motion exercises and weight bearing as tolerated by pain. The patient's condition has been followed for 16 months. He has returned to his former occupation of building silos, relating that 95% of his preoperative pain has been relieved with this procedure.

Case 2

The second patient is a 27-year-old counselor for mentally retarded children. While working with the Peace Corps in upper Volta in 1970, he fell approximately 60 feet, sustaining an injury to his right ankle. His initial treatment in North Africa consisted of splinting.

He was transferred to a European military hospital where the diagnosis of a tongue-depression type of calcaneal fracture was made. The involvement of the subtalar joint with the loss of his tuber-joint angle influenced his physician to attempt closed reduction. Using a Steinmann pin to control the fracture fragments, closed reduction was attempted with the patient under general anesthesia. After three unsuccessful attempts, the position was accepted. The patient was treated with a nonweightbearing cast for approximately eight weeks. At that time, the cast was removed and range-of-motion exercises were begun.

Three months after the injury, the patient was allowed to begin weight bearing as tolerated by pain. He had completed his tour of duty with the Peace Corps and had returned to civilian life. He noted that his left foot had become a limiting factor; for example, he was unable to walk barefoot on level ground without pain. The use of shoes allowed him to walk approximately 100 yards on level ground. Walking on grass was painful after several steps. He sought the opinion of an orthopedist who advised triple arthrodesis for the arthritic involvement of the subtalar joint.

The patient was seen in the Orthopedic Department of the Mayo Clinic for a second opinion regarding the pain he experienced in his left ankle with weight bearing. He walked with an antalgic limp but had a full range of motion of his ankle joint. Motion of the subtalar joint was limited and the area over the peroneal tendons at the level of the subtalar joint was tender to palpation. X-ray examination (Figure 4) revealed loss of the tuber-joint angle with subtalar joint

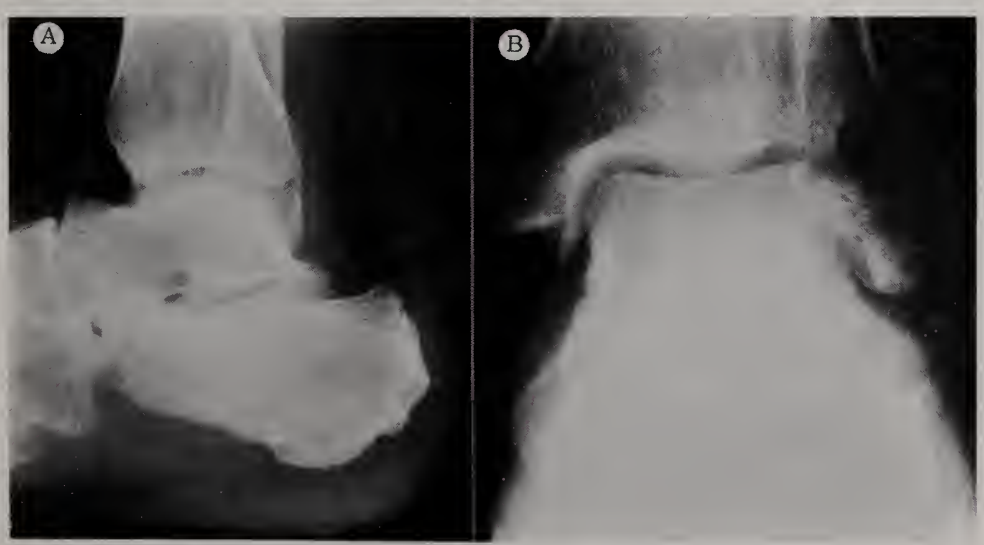


Fig. 4—(A) Lateral view showing changes in subtalar joint with loss of angle of inclination. (B) Anteroposterior view demonstrating hypertrophic lipping of subtalar joint (distal to lateral malleolus).

changes and widening of the calcaneus, especially on the lateral aspect.

Injection of the peroneal tendon sheath with 1% Xylocaine relieved 90% of the patient's pain. An additional 1 ml was injected into the heterotopic bone about the lateral aspect of the subtalar joint. After these two areas were injected, the patient related that he was able to walk on level ground barefooted and without pain. A tenogram was made. The dye was easily injected into the peroneal sheath, filling to the level of the subtalar joint. Examination of the tenogram demonstrated incomplete and irregular filling of the synovial sheaths of the peroneal tendons at the level of and distal to the level of the subtalar joint (Figure 5).

This patient was thought to have peroneal tendinitis, secondary to adhesions within the synovial sheath, and irritation from heterotopic bone about the subtalar joint as described by Kashiwagi and Inamatsu.[6] Surgical decompression of the tendon sheath together with removal of the heterotopic bone was recommended. The patient underwent this procedure, and his condition has been followed for 17 months. The pathologic changes noted at the time of operation were identical to those described with the first patient. The second patient related that he was completely free of pain except when engaging in strenuous physical activities such as tennis. After two hours of tennis, he experienced discomfort over the lateral aspect of his ankle, which he described as minor. He was able to carry on normal activities without discomfort.

Peroneal tendinitis after calcaneal fracture was described by Kashiwagi and Inamatsu.[6] This entity was first brought to my attention by Dr. Coventry, who has treated two patients with physical findings similar to those of the patients just described. His patients were treated in identical fashion and noted relief of their pain. Although this type of pain is not encountered in every patient with a calcaneal fracture, this is a syndrome that has not been fully appreciated by physicians treating patients with calcaneal fractures. Dr. Coventry, would you comment on this subject?

Dr. Mark B. Coventry:

I first became aware of this syndrome after a visit to Japan and seeing patients treated by Dr. Kashiwagi. I wonder how many patients have undergone triple arthrodesis who might have been relieved of their discomfort by a lesser procedure. The two patients discussed may or may not require arthrodesis in the future, but the tendon decompression should certainly be tried first.

Dr. Robert D. Beckenbaugh:

The patients you have presented were treated

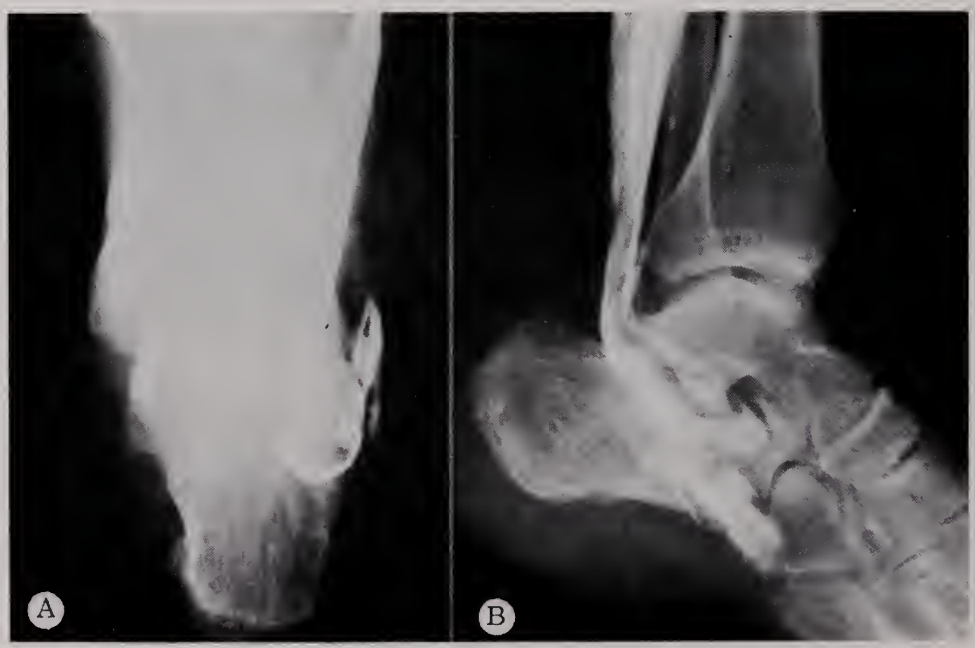


Fig. 5—Incomplete filling of peroneal tendon sheath at level of subtalar joint. (A) Calcaneus view and (B) lateral view.

by cast immobilization. Do you think this form of treatment might predispose to peroneal tendinitis?

Dr. Richard S. Bryan:

I have treated a patient with a calcaneal fracture with disruption of the subtalar joint by early motion in whom peroneal tendinitis has developed subsequently.

Dr. Fitzgerald:

Dr. Kashiwagi has made an important observation in noting that the tendinitis and adhesions are precipitated by the changes occurring in the lateral wall of the calcaneus and the heterotopic bone about the subtalar joint. Pain over the lateral aspect of the ankle and foot in a patient who has a healed calcaneal fracture should alert the physician to this syndrome.

Summary

Two patients treated for peroneal tendinitis after calcaneal fractures have been described. Both patients had their pain relieved after heterotopic bone was excised and the tendon sheaths decompressed. Although the frequency of this syndrome is unknown, physicians treating calcaneal fractures should be aware of its existence and management.

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6. Kashiwagi D, Inamatsu N: Diagnosis and treatment of fractures of the os calcis. Kobe J Med Sci Suppl 11:21, 1965.

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I have wondered whether cases like early chronic progressive cerebral sclerosis, or other brain lesions might be similarly helped.

R. L. Parsons, M.D.
Trimont, Minnesota

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	Starting Dosage	Increased Monthly by	Usual Maintenance	Maximal Recommended
Adult Hypercholesterolemic	1.0-2.0 mg.	1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac	0.5-1.0 mg.	1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as D-3,5,3′,5′-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following:
Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

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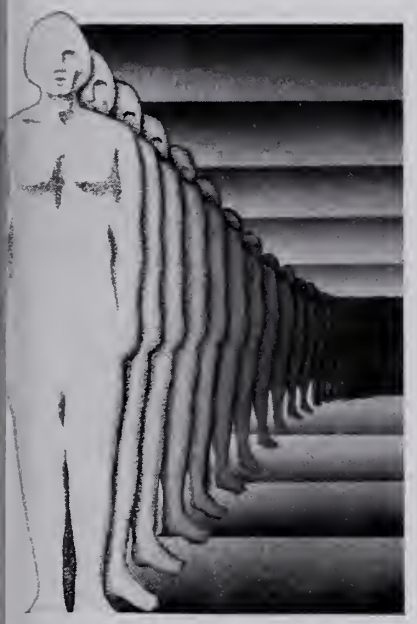
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Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.
Contraindications: Patients with known hypersensitivity to the drug.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

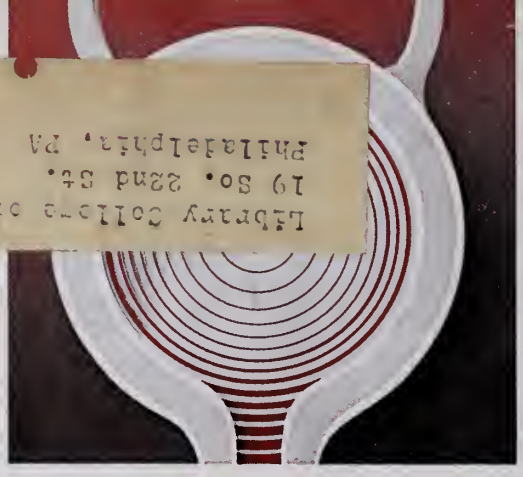
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety and tension, 5 to 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
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Indications: In adults, urinary tract infections complicated by pain (primarily cystitis, pyelitis and pyelonephritis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis,* and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. *Important Note:* Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response. Add aminobenzoic acid to culture media for patients already taking sulfonamides. Increasing frequency of resistant organisms currently is a limitation of the usefulness of antibacterial agents including the sulfonamides. Blood levels should be measured in patients receiving sulfonamides for serious infections, since there may be wide variations with identical doses; 12 to 15 mg/100 ml is considered optimal for serious infections; 20 mg/100 ml should be the maximum total sulfonamide level, as adverse reactions occur more frequently above this level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period. Contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with gastrointestinal disturbances, because of phenazopyridine HCl component.

Warnings: Safe use in pregnancy has not been established. Teratogenicity potential has not been thoroughly investigated. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported; clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts and urinalysis with careful microscopic examination should be performed frequently during sulfonamide therapy.

Precautions: Use with caution in patients with impaired renal or hepatic function, severe allergy, bronchial asthma and in glucose-6-phosphate dehydrogenase-deficient individuals. In the latter, hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme (Stevens-Johnson syndrome), skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis. *C.N.S. reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, polyarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide and thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Usual adult dosage for acute, painful phase of urinary tract infections is 4 to 6 tablets initially, then 2 tablets four times daily for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment of the infection with Gantrisin (sulfisoxazole) may be considered.

Note: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine soon after ingestion.

How Supplied: Tablets, each containing 0.5 Gm sulfisoxazole and 50 mg phenazopyridine HCl —bottles of 100 and 500.

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Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in s and/or severity of grand mal sei require increased dosage of star convulsant medication; abrupt w may be associated with tempora crease in frequency and/or seve seizures. Advise against simulta gestion of alcohol and other CNS sants. Withdrawal symptoms (si those with barbiturates and alco occurred following abrupt disco (convulsions, tremor, abdomina cle cramps, vomiting and sweat addiction-prone individuals und

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in the patient within a few days rather than in a week or two, although it may take longer in some patients. In addition, Valium (diazepam) is generally well tolerated; as with most CNS-acting agents, caution patients against hazardous occupations requiring complete mental alertness.

Also, because the psychoneurotic patient's symptoms are often intensified at bedtime, Valium can offer an additional benefit. An *h.s.* dose added to the *b.i.d.* or *t.i.d.* treatment regimen can relieve the excessive anxiety and associated depressive symptoms and thus encourage a more restful night's sleep.



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in psychoneurotic anxiety states with associated depressive symptoms

nce because of their predisposi-
abituation and dependence. In
cy, lactation or women of child-
age, weigh potential benefit
possible hazard.

ions: If combined with other psy-
ics or anticonvulsants, consider
y pharmacology of agents em-
drugs such as phenothiazines,
s, barbiturates, MAO inhibitors
r antidepressants may potentiate
n. Usual precautions indicated in
severely depressed, or with latent
ion, or with suicidal tendencies.
Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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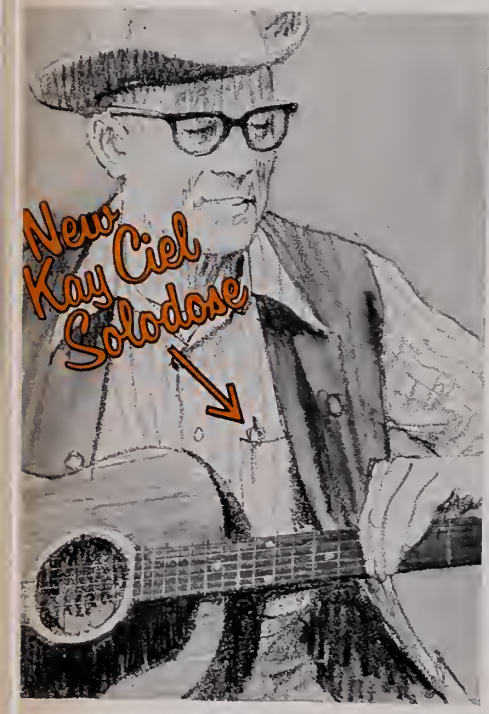
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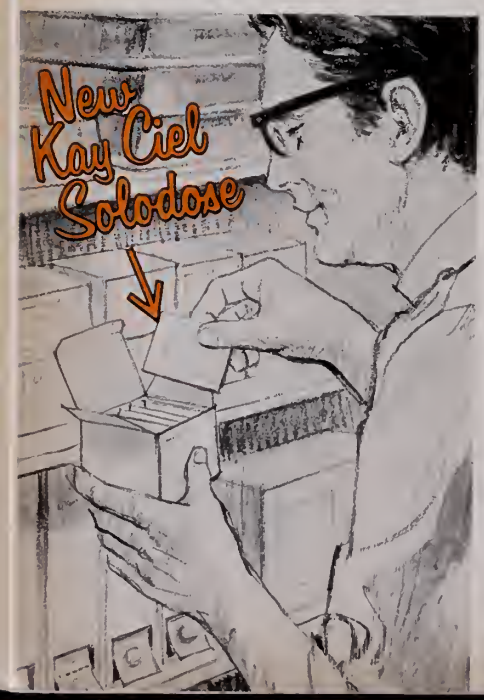












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Chairman's Letter

Minnesota State Medical Association Reorganization

(The "Entity")

Late in 1974, the Council of the Minnesota State Medical Association (M.S.M.A.) appointed an Ad Hoc Committee for the purpose of evaluating the structure and function of the M.S.M.A. This Committee has met from time to time throughout 1975 and began its work by examining such fundamental questions as to whether or not there was a reason for the continuing existence of the M.S.M.A. It rather quickly concluded that despite the existence of many strong and beneficial specialty and sub-specialty organizations, it did indeed remain a common denominator of Doctors of Medicine with its inherent commitment to the time honored moral commitments of professionalism. While wishing to aid and encourage the educational efforts of specialty societies, it was clear to all that an umbrella organization of all Doctors of Medicine in Minnesota was a continuing necessity.

It seemed to the Committee, that of high priority were: (1) The need for improved communication and liaison with the public. (2) The need for an improved avenue for flow of sentiment and power from the grass roots membership to a truly representative leadership charged with and empowered to act decisively for the membership. (3) And that in order to cope with the ever-broadening demands upon the society that an internal reorganization be accomplished in an attempt to enable the organization to function more efficiently.

Accordingly, the Committee recommended to the House of Delegates in May of 1975, that (1) a Citizen's Advisory Council be established. (2) an "Entity" be formed within the organization of the M.S.M.A. which would act as a physician's advocate in socio-economic affairs and that it be empowered to be an authoritative interface between governmental agencies, third party payors, and consumer groups. It would be responsible to the membership through the Council and ultimately the House of Delegates. (3) it additionally recommended to the House of Delegates that four other departments be created out of realignment of existing structure, namely: the Department of Administration, the Department of Membership Services, the Department of Public Education and the Department of Membership Education. The House of Delegates responded by approving these recommendations and specifically earmarked a $50.00 per annum dues increase for the implementation of the "Entity."

Subsequent to the House of Delegates, the Ad Hoc Committee has recommended to the Council, and the Council has approved, that the Entity be named the Department of Socio-Economic and Legislative Affairs. The new Department of Socio-Economic and Legislative Affairs demands appropriately designated hired staff assigned to it as do all departments. Staff department heads would report to the Executive Vice President or Executive Director which would be the new title of position formerly known as the Executive Secretary. The physician direction of the department would be headed by the President of the M.S.M.A. with the Vice Chairman being the President Elect and further mandated members being the Speaker of the House of Delegates and the Chairman of the Council. Additional membership of this Board would consist of one physician representative of each health service area designed within the state with the exception of the

metropolitan area which, since it accounts for nearly half of the physicians in the state, would have two representatives. It is intended that this body would utilize the vast talents of many of the organization's members and that the policies established within this department would directly reflect the consensus of opinion of the members on issues which it would represent in a democratic fashion. Feeling that the staff department head of the Department of Socio-Economic and Legislative Affairs is an extremely sensitive area requiring a number of specific qualities, Council has appointed a Search Committee to screen and recommend hiring of an individual for this position.

In a time when physicians need to vigorously reassert their influence on the development of health care policy, it is hoped that the above outlined realignment of our organization will allow us to more efficiently present our considered opinions in an accurate, responsible, and authoritative way. Success will depend largely upon the individual efforts and participation of all of the members. It must always be remembered that the real battles are fought on the national level, and it behooves each of us to individually support our national organization with our membership dollars and through this outlined reorganization to positively and constructively make the ideas of Minnesota Doctors clearly available to the national organization. Individuals and organizations who fail to aggressively assert themselves or offer their expertise quickly find themselves disgruntled spectators to the action of this consumer oriented society—even in the health care field.

Robert S. Flom, M.D.
Chairman
Ad-Hoc Committee to Council

Continuing Medical Education

University of Minnesota

Registration information: Office of Continuing Medical Education, University of Minnesota, 143 Oure Hall, Box 293, the Medical School, Minneapolis 55455, or by phone (612) 373-8012. Courses offered are:

Colon and Rectal Surgery—November 5-7, 1975—Mayo Memorial Auditorium, University of Minnesota. Fee: $150.00.

This course appeals to a national audience of surgeons whose practice includes colon and rectal procedures.

Refraction for the Non-Ophthalmologist—November 12-14, 1975—University Hospital, University of Minnesota. Fee: $150.00.

Physicians who wish to add refraction to the scope of their practice will be interested in this course.

Economic and Legal Aspects of Modern Office and Clinic Practice—November 21-22, 1975.

The business side of medical practice is a complex and compelling reality. Partnership and organizational arrangements, legal documents and procedures, office and personnel, policies and methods, are of interest to many physicians.

Practical Ophthalmology in Primary Care—December 8-9, 1975—Sheraton-Ritz Hotel. Fee: $100.00.

Examination of the eye, and care of emergencies involving the eye are emphasized

The continuing medical education programs of the University of Minnesota Medical School have been accredited by the Council on Medical Education of the American Medical Association and are acceptable for credit toward the American Medical Association's Physician's Recognition Award.

Editor's Notebook

Better Read than Dead

". . . doubt has been raised as to the future of reading—whether the printed word is on its last legs."—E. B. White, *The Second Tree from the Corner,* Harper & Row. 1954

Doubt has also been raised as to the future of State Medical Journals. The reasons for this doubt are easy to understand: (1) more competition for physicians' reading time; and (2) less advertising revenue to support journals. Physicians already have a lot to read—specialty journals, throwaway magazines, drug house releases, hospital memoranda, and medical newsletters. And in most states, advertising revenues continue to shrink while publishing costs swell.

Small wonder, then, that some State Journals are in trouble.

As for MINNESOTA MEDICINE, two recent events—a State Medical Journal Advertising Bureau meeting in Chicago and the response to our September MINNESOTA MEDICINE questionnaire—give promise for the future.

Advertising

At the Chicago meeting, I learned that Minnesota ranks fourth this year compared to last year among 34 journals in percent gain in national advertising. In the first ten months of 1975 compared to the first ten months of 1974, our advertising went up by 17 percent. This increase pleased me because the Board of Editors and myself have been working hard this year to step up our national, local, and classified advertising. (Incidently, if you have something to sell, such as a vacation home, a vintage automobile, office equipment, medical instruments, or if you are seeking an associate, we would appreciate your placing an ad in our classified section. You too, you see, can help.)

Why have we concentrated on increasing our advertising revenues? Because I would like the Journal to be as economically self-reliant as possible. There are limits to how self-sufficient we can be, but we want you to know we are trying. Also more advertising will decrease the small portion of your dues devoted to MINNESOTA MEDICINE. In 1974, just over *five percent* of your annual dues went to support the journal. In 1975, because of the jump in your dues and our increased advertising revenue, this figure may drop to close to *three percent* of your yearly dues. Which isn't much, especially when you consider publishing costs rise 10 percent per year, and when you realize MINNESOTA MEDICINE is the main artery of communication for the Minnesota Medical Association.

Questionnaire

The advertising picture encourages me but what delights me even more is the uninhibited way you responded to our September questionnaire. Seventy questionnaries found their way back to my desk. From the items you checked and from

your comments, I can see MINNESOTA MEDICINE is being read. And from the tone of your comments, I gather we are not only alive but lively.

That's a good sign. For we want a journal that is controversial enough to get your attention but conservative enough to gain your respect. To find that middle ground, we used the questionnaire to sample your opinions and to find where we stand.

Perhaps at this point, I should go through the questionnaire question by question. This process gives me the opportunity to review answers, share compliments, answer critics, confess limitations, and maybe even make a few comments.

1. Do you read MINNESOTA MEDICINE?

	Number of Readers	Percent of Readers
Not at all	2	3%
25%	18	26%
50%	20	29%
75%	20	29%
Entirely	10	13%

2. Which of the following sections in MINNESOTA MEDICINE do you read?

Scientific	54	77%
Editorials	55	79%
Letters to the Editor	38	54%
Editor's Notebook	47	67%
Quotes at the bottom of articles	38	54%
Full page fillers	16	23%
X-ray and Scan Conferences	27	38%
President's Letter	41	58%
Fracture Conferences	23	33%
Special Issues	39	56%
CPC	29	41%
Grand Rounds	26	37%
Special Articles	41	58%
Continuing Education	33	47%
Laboratory Medicine	35	50%
Dermatology	18	26%
Book Reviews	31	44%
History of Medicine	31	44%
In Memoriam	37	53%

I find these figures interesting for these reasons. In the first place, about 70 percent of readers say they read at least half of the articles. Because you are busy people, I consider that good readership. Secondly, you tend to stick to scientific articles (77 percent) or to editorial comment on those articles (79 percent). Third, you like to read on occasion the President's Letter (59 percent), the Editor's Notebook (67 percent), and Special Articles (58 percent). After that, the distribution of your likes and dislikes becomes too widely dispersed for me to interpret.

So much for statistics, now for your suggestions.

In our questionnaire, we asked: "Do you have any suggestions on how we might improve MINNESOTA MEDICINE?" Here, for your perusal, are a few of your suggestions and my comments:

Suggestions	Comments
Include a question and answer section to which a physician could send a question (on medicine or economics) and receive an answer in a reasonable time.	Why not? *JAMA* has such a section, and we are not averse to discussing economic matters.
That I might continue to receive MINNESOTA MEDICINE for some time, for an indefinite period of time.	'Til death do us part.
Show us how to fill in the forms for Continuing Education that we are supposed to send to MSMA. How much detail?	We'll check and write you.

Brevity is the soul of wit. Three cheers for Dr. Reece.	Speaking of brevity, I'm reminded of a three word history of microbiology: "Adam had 'em."
Better format . . . It's really a waste now . . . To hell with pretty pictures on front.	A minority retort. Most speak highly of our covers.
I enjoy every issue.	Thank you.
More courageous, direct, analytical and questioning editorials on strengths and limits of medical system and established medicine.	Good idea. We're taking steps in this direction (see page 851 in this issue).
Its diversity is a plus.	Variety is the spice.
Photographic duplication of X-rays lacks detail. Need to improve quality of photos.	We get the picture.
We need articles of a fundamental physiologic nature that will be of use to almost all doctors, regardless of specialty.	Who doesn't? We'll accept any or all that do.
I read it, JAMA, and the *New England Journal.*	Good for you. Incidently, we're proud to be in such select company.
I believe MINNESOTA MEDICINE nicely fulfills the needs of the varied medical audience it serves.	I trust fulfilling needs is the same as satisfying wants.
Must keep bibliography with article.	We do and have for the last four years.
Keep after good studies. Signed: An allergist.	We are not allergic to good studies.
More broad based reviews.	Too often broad reviews turn into long rehashes. Besides, we have purposefully limited our space to cut down expenses.
I have always been pleased with MINNESOTA MEDICINE. It is not the NEW ENGLAND JOURNAL OF MEDICINE, nor is it supposed to be.	No, but maybe some day it will be the MIDWESTERN JOURNAL OF MEDICINE.

And there you have it—a smattering of your responses to our recent questionnaire. We appreciate your taking the time to fill in the form and to keep us on our toes. Better on our toes than on our last legs.

Richard L Reece MD



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We help you help.

An employee of yours has a house fire, a disabled parent, an emergency of any kind.

That's when Red Cross—America's Good Neighbor—steps in to lend a hand. Because helping people is what we're all about.

You could say all this helps your company, too.

Because easing people over life's rough spots makes them easier in their minds. And no one has to tell you how important that is on the job.

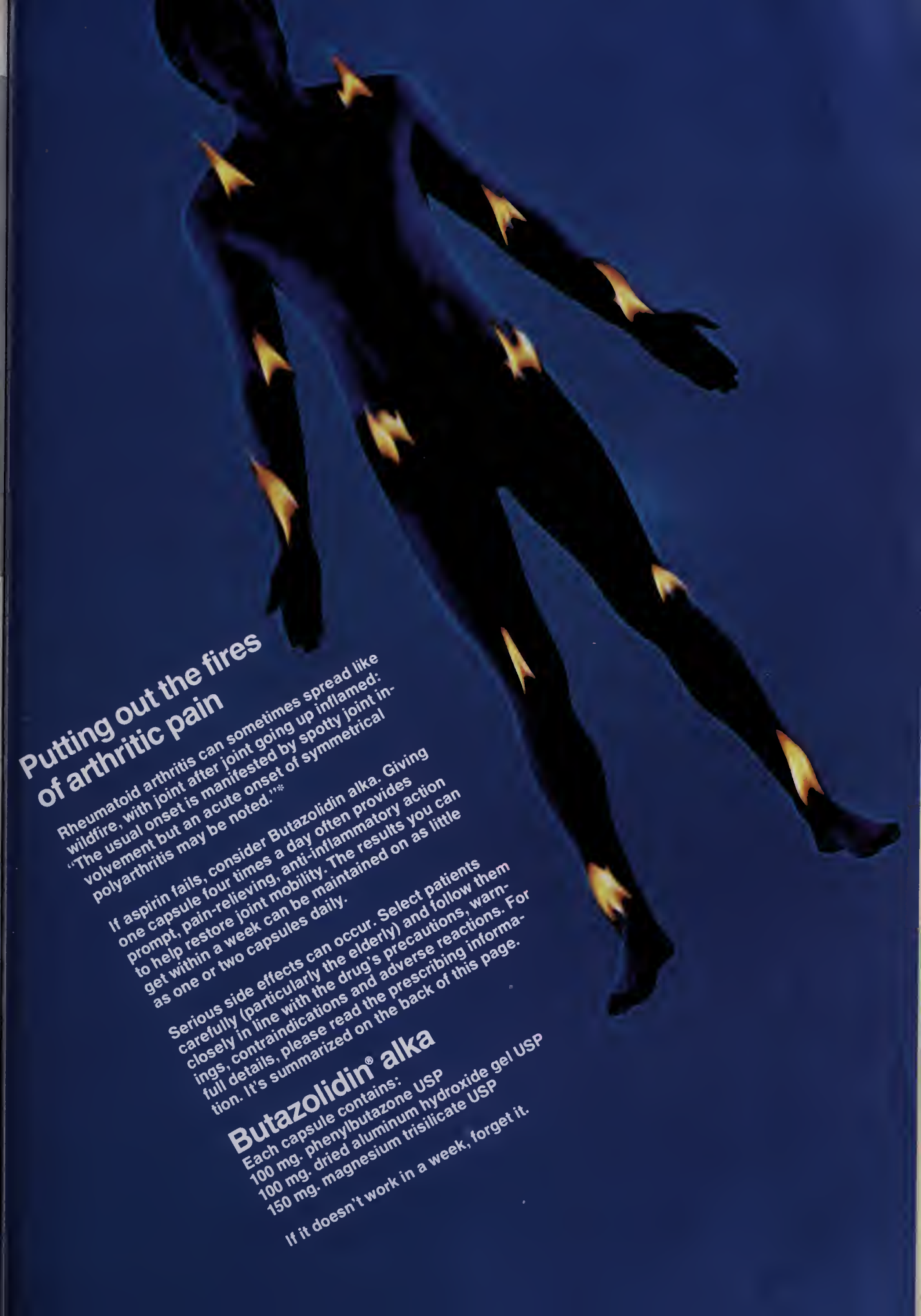
So help Red Cross any way you can.

When you help us, it helps your people.

And when you help your people, you help yourself.



Red Cross. The Good Neighbor.



Putting out the fires of arthritic pain

Rheumatoid arthritis can sometimes spread like wildfire, with joint after joint going up inflamed: "The usual onset is manifested by spotty joint involvement but an acute onset of symmetrical polyarthritis may be noted."*

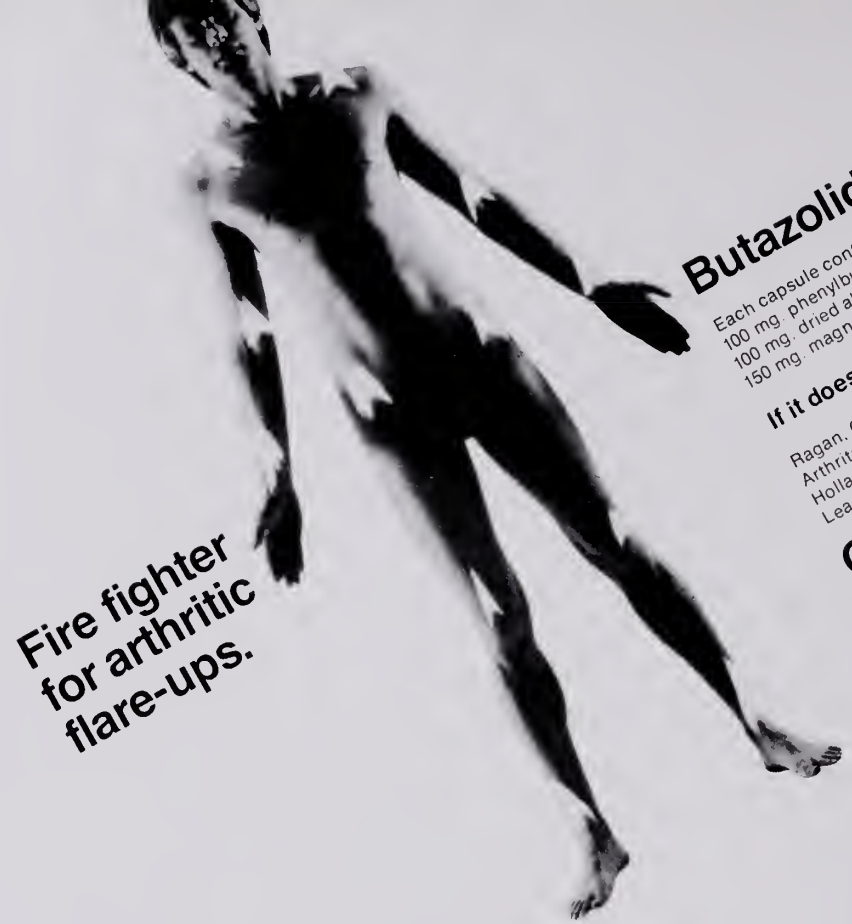
If aspirin fails, consider Butazolidin alka. Giving one capsule four times a day often provides prompt, pain-relieving, anti-inflammatory action to help restore joint mobility. The results you can get within a week can be maintained on as little as one or two capsules daily.

Serious side effects can occur. Select patients carefully (particularly the elderly) and follow them closely in line with the drug's precautions, warnings, contraindications and adverse reactions. For full details, please read the prescribing information. It's summarized on the back of this page.

Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.



Butazolidin® alka

Each capsule contains:
100 mg. phenylbutazone USP
100 mg. dried aluminum hydroxide gel USP
150 mg. magnesium trisilicate USP

If it doesn't work in a week, forget it.

Ragan, C.: The Clinical Picture of Rheumatoid Arthritis, in Arthritis, ed. 8, edited by J. L. Hollander and D. J. McCarty, Jr., Philadelphia, Lea & Febiger, 1972, chap. 21, p. 335.

Geigy

Fire fighter for arthritic flare-ups.

Important Note This drug is not a simple analgesic Do not administer casually Carefully evaluate patients before starting treatment and keep them under close supervision. Obtain a detailed history, and complete physical and laboratory examination (complete hemogram, urinalysis, etc.) before prescribing and at frequent intervals thereafter Carefully select patients, avoiding those responsive to routine measures, contraindicated patients or those who cannot be observed frequently Warn patients not to exceed recommended dosage Short-term relief of severe symptoms with the smallest possible dosage is the goal of therapy Dosage should be taken with meals or a full glass of milk Substitute alka capsules for tablets if dyspeptic symptoms occur Patients should discontinue the drug and report immediately any sign of fever, sore throat, oral lesions (symptoms of blood dyscrasia); dyspepsia, epigastric pain, symptoms of anemia, black or tarry stools or other evidence of intestinal ulceration or hemorrhage, skin reactions, significant weight gain or edema A one-week trial period is adequate Discontinue in the absence of a favorable response Restrict treatment periods to one week in patients over sixty

Indications Rheumatoid arthritis, osteoarthritis, bursitis acute gouty arthritis and rheumatoid spondylitis

Contraindications Children 14 years or less, senile patients, history or symptoms of G I inflammation or ulceration including severe, recurrent or persistent dyspepsia history or presence of drug allergy, blood dyscrasias, renal, hepatic or cardiac dysfunction, hypertension, thyroid disease, systemic edema, stomatitis and salivary gland enlargement due to the drug polymyalgia rheumatica and temporal arteritis, patients receiving other potent chemotherapeutic agents, or long-term anticoagulant therapy

Warnings Age, weight dosage, duration of therapy, existance of concomitant diseases, and concurrent potent chemotherapy affect incidence of toxic reactions Carefully instruct and observe the individual patient, especially the aging (forty years and over) who have increased susceptibility to the toxicity of the drug Use lowest effective dosage Weigh initially unpredictable benefits against potential risk of severe, even fatal, reactions The disease condition itself is unaltered by the drug Use with caution in first trimester of pregnancy and in nursing mothers Drug may appear in cord blood and breast milk Serious, even fatal, blood dyscrasias, including aplastic anemia, may occur suddenly despite regular hemograms, and may become manifest days or weeks after cessation of drug Any significant change in total white count, relative decrease in granulocytes, appearance of immature forms, or fall in hematocrit should signal immediate cessation of therapy and complete hematologic investigation Unexplained bleeding involving CNS, adrenals and G I tract has occurred The drug may potentiate action of insulin sulfonylurea, and sulfonamide-type agents. Carefully observe patients taking these agents. Nontoxic and toxic goiters and myxedema have been reported (the drug reduces iodine uptake by the thyroid) Blurred vision can be a significant toxic symptom worthy of a complete ophthalmological examination Swelling of ankles or face in patients under sixty may be prevented by reducing dosage If edema occurs in patients over sixty, discontinue drug

Precautions The following should be accomplished at regular intervals Careful detailed history for disease being treated and detection of earliest signs of adverse reactions, complete physical examination including check of patient s weight, complete weekly (especially for the aging) or an every two week blood check, pertinent laboratory studies Caution patients about participating in activity requiring alertness and coordination, as driving a car, etc Cases of leukemia have been reported in patients with a history of short- and long-term therapy The majority of these patients were over forty Remember that arthritic-type pains can be the presenting symptom of leukemia

Adverse Reactions This is a potent drug, its misuse can lead to serious results Review detailed information before beginning therapy Ulcerative esophagitis, acute and reactivated gastric and duodenal ulcer with perforation and hemorrhage, ulceration and perforation of large bowel, occult G I bleeding with anemia, gastritis, epigastric pain, hematemesis, dyspepsia, nausea, vomiting and diarrhea, abdominal distention, agranulocytosis, aplastic anemia, hemolytic anemia, anemia due to blood loss including occult G I bleeding, thrombocytopenia, pancytopenia, leukemia, leukopenia bone marrow depression, sodium and chloride retention, water retention and edema, plasma dilution, respiratory alkalosis, metabolic acidosis, fatal and nonfatal hepatitis (cholestasis may or may not be prominent), petechiae, purpura without thrombocytopenia toxic pruritus, erythema nodosum, erythema multiforme, Stevens-Johnson syndrome, Lyell's syndrome (toxic necrotizing epidermolysis), exfoliative dermatitis, serum sickness, hypersensitivity angiitis (polyarteritis), anaphylactic shock, urticaria, arthralgia, fever, rashes (all allergic reactions require prompt and permanent withdrawal of the drug) proteinuria hematuria, oliguria, anuria, renal failure with azotemia, glomerulonephritis, acute tubular necrosis, nephrotic syndrome, bilateral renal cortical necrosis, renal stones, ureteral obstruction with uric acid crystals due to uricosuric action of drug, impaired renal function, cardiac decompensation, hypertension, pericarditis, diffuse interstitial myocarditis with muscle necrosis, perivascular granulomata, aggravation of temporal arteritis in patients with polymyalgia rheumatica, optic neuritis, blurred vision, retinal hemorrhage, toxic amblyopia, retinal detachment, hearing loss, hyperglycemia, thyroid hyperplasia, toxic goiter, association of hyperthyroidism and hypothyroidism (causal relationship not established), agitation, confusional states lethargy, CNS reactions associated with overdosage including convulsions, euphoria, psychosis, depression, headaches, hallucinations, giddiness, vertigo, coma, hyperventilation, insomnia, ulcerative stomatitis, salivary gland enlargement.

(B)98-146-070-J (10/71)

For complete details, including dosage, please see full prescribing information.

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Division of CIBA-GEIGY Corporation
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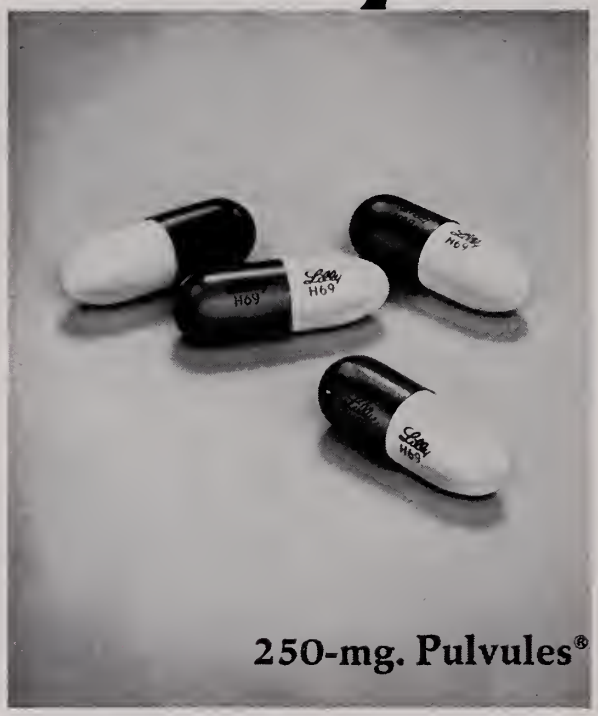
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Virus Infections and Kidney Disease

RICHARD J. HOWARD, M.D.* and HENRY H. BALFOUR, JR., M.D.*

The only virus which consistently causes acute renal malfunction is the arbovirus of epidemic hemorrhagic fever. Chronic glomerulonephritis has been associated with virus (antigen)-antibody complexes in animal models. The possibility that immune complexes involving viruses may be responsible for human glomerulonephritis is suggested by preliminary data on patients with chronic serum hepatitis (hepatitis B) infections.

VIRAL INFECTION can cause both transient and chronic renal malfunction. Transient abnormalities in kidney function, hematuria, and proteinuria occurring during the course of acute systemic viral infections have been documented for many years.[1,2] Viral infections as the etiology of chronic renal disease have received attention only recently. The purpose of this review is to summarize the association of virus infections and renal disease in man.

Transient Renal Abnormalities Associated with Acute Viral Infections

Temporary renal abnormalities may occur with illnesses of varied etiology (Table).[3-5] These temporary abnormalities include changes in renal function as manifested by elevation of the serum creatinine and blood urea nitrogen (BUN) and decreased creatinine clearance, proteinuria, hematuria, and alterations in the urine sediment. Renal malfunction during an acute viral infection may not necessarily be due to direct viral infection of the kidney. Rather, it may be due to release of "toxic" products from other tissues infected by the virus or from physiological changes due to the infection. Viruses may be cultured from kidney tissue or the urine and viral inclusion bodies can be seen in histologic specimens without associated changes in renal function, proteinuria, or hematuria. Viruria is a common feature of virus infection, and isolation from the urine is a standard diagnostic test for congenital rubella and cytomegalovirus infection. Many other viruses including measles, vaccinia, coxsackievirus, polio, mumps, and echoviruses have also been recovered from the urine during specific infections.[1,2]

TABLE
Virus Infections Associated with Transient Renal Abnormalities

Echovirus Types 6 and 9
Coxsackievirus Group B
Mumps
Adenovirus
Vaccinia
Varicella Zoster
Hepatitis A
Influenza
Cytomegalovirus
Arbovirus of epidemic hemorrhagic fever

Sabin et al.[6] observed microscopic hematuria in nearly 50 percent and proteinuria in 10 percent of the patients during an echovirus Type 9 epidemic. These changes occurred only during the febrile phase of the illness. Two cases of acute glomerulonephritis in two-and-a-half-year-old identical twin boys associated with echovirus 9 infection were reported by Yuceoglu et al.[7] Renal biopsy demonstrated hypercellular glomeruli and obliteration of Bowman's space. The patients had mild proteinuria and microscopic hematuria for one week after the onset of the illness. Mary and Swallow[8] reported proteinuria and hematuria in one patient during an epidemic of aseptic meningitis, pharyngitis, and myalgia due to echovirus Type 6 infection. The patient recovered in five days with no apparent sequelae. Since the authors reported only one case of renal abnormality during

*Departments of Surgery, Laboratory Medicine and Pathology, and Pediatrics, University of Minnesota Health Sciences Center, Minneapolis, Minnesota 55455.
Address reprint requests to: Dr. Balfour at Box 437 Mayo, University of Minnesota Hospitals, Minneapolis, Minnesota 55455.
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See editorial, page 831.

an epidemic of echovirus six infection, renal dysfunction must be very uncommon with this virus infection.

Group B coxsackieviruses have been found in the urine during clinical infection manifested by meningoencephalitis and myalgia.[9,10] Hinuma et al.[11] demonstrated coxsackievirus B5 viral antigen by immunofluorescence in exfoliated cells in the urinary sediment of six of 12 patients with meningoencephalitis suggesting multiplication of virus in cells of the urinary tract. Hematuria, proteinuria, or other renal abnormalities were not mentioned in the above reports. However, decreased PSP excretion has been reported in coxsackievirus infection during the period when virus was cultured from the urine.[2] Burch and Colcolough[12] recently described a 45-year-old male who died of pancarditis due to coxsackievirus B4. This patient also had persistent hematuria, proteinuria, and progressive deterioration of renal function. The BUN increased to 55 mg per 100 ml and the creatinine to 2.5 mg per 100 ml. Postmortem examination revealed focal glomerulonephritis and interstitial nephritis. Coxsackievirus B4 antigen was demonstrated in the glomeruli and interstitium by immunofluorescence.

Mumps virus has regularly been isolated from the urine during the early stages of mumps parotitis.[13,14] The duration of viruria rather than the febrile period is correlated with a decreased creatinine clearance.[13] The creatinine clearance was decreased in 17 of 20 patients with mumps parotitis. Thomas et al.[15] also noted a transiently decreased creatinine clearance in two sisters with paralytic mumps virus infection. The serum creatinine and BUN were normal, however. Fatal nephritis and acute glomerulonephritis associated with mumps occurred in two children.[16]

All other cases of renal abnormalities in association with mumps virus infection have been temporary and without sequelae.

Adenoviruses have also been cultured from the urine, and infection has been associated with temporary renal disturbances. Hematuria was observed in many patients in an epidemic of pharyngoconjunctival fever caused by adenovirus Types 3 and 4.[17] Five of 27 children having pneumonia due to adenovirus Type 7 were thought to have signs of acute glomerulonephritis.[18] An epidemiological investigation has found a higher incidence of nephritis in patients with evidence of adenovirus infection compared to the normal population.[2] Experimental studies have also implicated adenoviruses in the etiology of kidney disease. Ginder[19] found murine adenoviruses in the mouse kidney 70 days after intraperitoneal infection. Cellular infiltrates and moderate tubular damage were observed at this time. The virus predisposed the mice to pyelonephritis by intravenously administered *E. coli.*

Acute glomerulonephritis and acute tubular necrosis have been reported to occur after primary vaccinia inoculation and revaccination.[1] Herbut[20] reported a case of fatal glomerulonephritis in a 64-year-old man seven days following revaccination. Autopsy showed glomerular endothelial and epithelial proliferation and inflammatory infiltrate. However, the glomerulonephritis was thought to be due to an allergic reaction because of the long period between revaccination and onset of disease. This case of glomerulonephritis could represent an immune complex glomerulonephritis as will be discussed in the next section.

Yuceoglu et al.[21] reported acute glomerulonephritis in three patients with chickenpox (varicella). All three had mild to moderate proteinuria in association with or prior to the onset of the rash. The BUN rose to 50 mg per 100 ml and the creatinine clearance fell to 39 ml per min in one patient. Others[22-24] have also reported the association of acute glomerulonephritis and nephritis with varicella infection.

Infectious hepatitis (hepatitis A) has also been associated with transient hematuria and proteinuria.[25] Renal biopsies from patients with hepatitis showed swelling of the tubular epithelium and hypercellularity of the glomeruli. None of the patients had residual renal malfunction or histologic changes on rebiopsy one year later. Others, however, have attributed the renal malfunction and histologic changes to toxic products from infected tissues rather than to direct viral invasion of the kidneys.

Acute nephritis and glomerulonephritis have been associated with influenza virus infection. The virus has been isolated from the kidneys of patients who died with influenza, and it has been cultured from the urine of patients with the clinical disease.[2] Several cases of acute interstitial nephritis and hemorrhagic glomerulonephritis occurring as complications of influenza virus infection have been reported.[2,26]

Cytomegalovirus (CMV) has been repeatedly isolated from kidney specimens and from the urine, and typical inclusion bodies frequently can be seen in histologic sections of the kidneys from infected patients and epithelial cells in the urine sediment. CMV has received additional attention in recent years because of its high incidence of infection in kidney transplant recipients. In these patients CMV infection has been implicated in the death of some transplant recipients and has been associated with renal malfunction, thought possibly due to transplant rejection triggered by the virus.[27]

While virus infections may cause temporary renal malfunction, only rarely do they cause progressive or fatal renal disease. The examples of transient renal abnormalities associated with viral infection described above are isolated case reports. The great majority of these virus infections are not associated with kidney malfunction. In those cases with renal malfunction there seldom has been proof that the abnormalities were due to direct viral invasion of renal tissue. On the other hand, culturing virus from the urine in a patient who has temporary renal malfunction also does not prove that the virus is responsible for any renal abnormalities.

Unlike the sporadic instances of renal malfunction with many viral illnesses, infections with the arbovirus causing epidemic hemorrhage fever are frequently associated with development of renal failure. Rapidly progressive renal failure caused by the epidemic hemorrhagic fever virus has been described for many years but it did not become widely known to the American medical profession until the Korean War.[28] Hemorrhagic fever is characterized by a three to eight-day febrile phase, an oliguric phase, and then a diuretic phase with recovery.[29] Marked proteinuria and hematuria precede the oliguric phase. Kidney biopsy and autopsy specimens show acute tubular necrosis and hemorrhage limited to the corticomedullary zone.[30] Patients who recovered had normal renal function. Hemorrhagic fever and acute renal failure has also been described in American troops in Vietnam.[31] Renal failure has been the cause of death in some of these patients.

Chronic Glomerulonephritis Associated with Viral Infections

Antigen-antibody complexes can cause chronic glomerulonephritis.[32] The immune complexes activate the complement system and cause an immune glomerulonephritis.

Viruses may exist in the circulation in the form of virus (antigen)-antibody complexes. Infectious virus-antibody complexes have been demonstrated in the blood of animals infected with murine leukemia virus, lactic dehydrogenase virus (LDV), lymphocyte choriomeningitis virus (LCM), Aleutian disease of mink virus, and equine infectious anemia virus.[33] In addition to infectious virus-antibody complexes, other viral coded antigens such as nonstructural proteins, viral nucleic acid, and viral enzymes may contribute to the pool of complexes.

Hotchin[34] first demonstrated that infection of newborn mice with LCM established a chronic infection which eventually led to glomerulonephritis. Oldstone and Dixon[35] subsequently demonstrated that LCM virus existed in the blood as an infectious virus-antibody complex in chronically infected mice and that the kidneys contained large amounts of LCM antigen, anti-LCM antibody, and complement. Histologic studies revealed changes typical of chronic glomerulonephritis. Whereas LCM produces a severe glomerulonephritis, LDV, which also exists as infectious virus-antibody complexes in the blood of infected mice, causes only a mild glomerulonephritis. Why one virus causes severe glomerulonephritis whereas another produces mild glomerulonephritis is not known.

The possibility that immune complexes involving viruses may produce human glomerulonephritis is now being actively investigated. Immune complexes in the glomeruli of patients with chronic serum hepatitis (hepatitis B) are well documented.[36,37] Combes et al.[38] reported chronic membranous glomerulonephritis developing in post transfusion hepatitis. Australia antigen (HB_sAg), IgG, and B_1C (complement) were found in the glomeruli by immunofluorescent studies. Myers et al.[39] and Nowaslowski et al.[40] also reported chronic membranous glomerulonephritis in patients with chronic active hepatitis and chronic aggressive hepatitis. Nowoslawski et al.[40] described the localization of Australia antigen-antibody complexes in the arteries of the kidneys.

Bryosko et al.[41] examined kidney biopsies from 52 unselected cases of clinically diagnosed ne-

phrosis and/or glomerulonephritis in children. Immunoglobulins (IgG, IgM, and IgA) and complement were detected by immunofluorescence in 32 of the 53 biopsies. Deposits with the composition of hepatitis B surface antigen-antibody complexes were identified in 18 of these 32 specimens. Bajtai et al.[42] have described similar findings in the kidney in a patient who developed cirrhosis due to hepatitis B.

Lagrue et al.[43] found hepatitis B antigenemia in 6.8 percent of 160 patients with chronic glomerulonephritis compared with an incidence of 0.54 percent in patients with various nephropathies and blood donors. The authors did not compare the two groups with respect to number of blood transfusions, however. Since one would expect patients with chronic renal disease to have received more blood transfusions than the control group, it is not surprising that a higher incidence of hepatitis B antigenemia was found. The findings do not necessarily implicate hepatitis B in the etiology of glomerulonephritis.

Dengue and respiratory syncytial viruses also exist in the blood as viral antigen-antibody complexes.[33] Investigations are currently underway to determine whether these viral immune complexes are the cause of chronic renal disease.

Discussion

Acute viral infections causing renal dysfunction and renal failure have thus far been described in articles reporting one or two cases. Very few epidemiological studies linking the incidence of renal dysfunction with various viral illnesses have been reported. The frequency of renal malfunction during the course of a viral infection might prove to be higher than the current literature would suggest if routine screening were done.

Current data suggest that with the exception of the arbovirus-caused epidemic hemorrhagic fever, renal dysfunction is a relatively rare complication of most acute viral infections.

Much interest has recently developed concerning the role of chronic viral infections in the etiology of chronic glomerulonephritis. With the findings that viruses can exist as circulating virus-antibody complexes and that these complexes can cause glomerulonephritis in experimental animals, attention has naturally focused on the search for similar immune complexes in humans. It is certainly reasonable to postulate that some cases of chronic glomerulonephritis in humans are also caused by viral-antibody complexes.

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30-43. Will be found on page 834.

Serum Alpha-Fetoprotein and Beta-Human Chorionic Gonadotropin Levels in Patients with Non-Seminomatous Germ Cell Testicular Cancer

PAUL H. LANGE, M.D.;* THOMAS R. HAKALA, M.D.;* and ELWIN E. FRALEY, M.D.*

Sera from 146 patients with genito-urinary disease were assayed for the presence of AFP and B-HCG by recently developed radioimmune assays. Levels of these markers were elevated almost exclusively in patients with non-seminomatous germ cell cancer of the testicle, and elevation of one or both of these serum markers correlated highly with the presence of active neoplastic disease. The use of these new serum assays for AFP and B-HCG may have broad applications both to the diagnosis and management of certain testicular neoplasms.

MUCH EFFORT HAS been devoted to the development of a specific serological test for the diagnosis of human cancer. Even though this goal has not been achieved, certain cancer-associated products have been detected in human serum using immunologic techniques, and such tests have proven useful in the detection and management of some malignancies. For example, a fetal antigen designated carcinoembryonic antigen (CEA) is elevated in the sera of some patients with gastrointestinal cancers. Although measurement of CEA does not seem useful as a screening test of these cancers, the level of CEA often: (1) correlates with the extent of the disease. (2) disappears with removal of the malignancy, and (3) increases prior to clinical evidence of recurrence.[1] Two other so-called markers of human malignancy, which actually were discovered before CEA, are serum alpha fetoprotein (AFP) and human chorionic gonadotropin (HCG). Either of these markers may be elevated in patients with non-seminomatous germ cell tumors of the testicle. The recent development of the more sensitive radioimmune assays to measure AFP and the beta glycoprotein chain of HCG (B-HCG) enhances the possibility that such assays will be useful in the management of these cancers.[2-4] This report will present the results of AFP and B-HCG determinations in serum from 146 patients with genitourinary disease and will illustrate the potential usefulness of these recently developed serum tests.

Methods

Since 1971, serum from 146 patients with various genitourinary diseases were obtained and

TABLE 1
Patient Population, AFP, and B-HCG Levels

Diagnosis	Number of Patients	Elevated AFP	Elevated B-HCG
hypernephroma	50	0	3*
transitional cell carcinoma	46	0	3*
adenocarcinoma of prostate	7	0	0
squamous cell carcinoma of penis	4	0	0
non-neoplastic genito-urinary diseases	12	0	0
germ cell testicular tumors			
seminoma	5	0	0
non-seminoma	22	12	6†

*below 10 mI.U. per ml.
†6/18 positive, all greater than 10 mI.U. per ml.

*Department of Urologic Surgery, University of Minnesota, College of Health Sciences, Minneapolis, Minnesota.
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See editorial, page 831.
*All radioimmune assays for AFP and B-HCG were performed by Dr. Thomas Waldmann, National Institutes of Health, Bethesda, Maryland.
†Kallestad Laboratories, Chaska, Minnesota.

stored in a liquid nitrogen freezer (−270°) (Table 1). Patients were designated as having "active disease" if they had pathological or radiographic evidence of tumor at the time the serum was obtained.

The sera of all patients were assayed for AFP using a radioimmune assay* as previously described.[5] This assay has a sensitivity of five nanograms (10^{-9} grams) per milliliter (ng per ml), and levels greater than 40 ng per ml. are considered abnormal for individuals over one year of age. The sera of many patients were also assayed for AFP by the immunoelectro-osmophoresis assay which employs commercially available reagents,† Beta human chorionic gonadotropin levels also were determined* by a radioimmune assay as previously described.[6] The B-HCG assay has a sensitivity of five milli-International Units (mI.U.) per ml., which is at least 200 times more sensitive then the commonly used urinary assays such as the agglutination inhibition "immunoassay" for HCG.

Results

As demonstrated in Table 1, elevated AFP values were found only in patients with non-seminomatous germ cell tumors of the testicle, and were not present in 124 patients with other genitourinary diseases. Beta-human chorionic gonadotropin was detected occasionally in other genitourinary cancers, as has been reported previously,[3] but levels greater than 10mI.U. per ml. were found only in testicular tumor patients.

TABLE 2
Determination of AFP by AGAR-Gel Precipitation vs. Radioimmune Assay Methods

Patient	AFP IEOP[1]	AFP RIA (ng/ml.)
27S	−	29
97W	−	1200*
100A	−	19
39D	−	29
1F	−	60*
284F	−	14
37H	−	255*
35H	−	175*
34J	−	70*
380Z	−	19
33K	+	>90,000*
415B	+	3600*
665P	±	1500*
664B	−	135*
271M	−	750*

[1]Immunoelectroosmophoresis (Kallestad Labs.)
*Positive (> 40 ng per ml.)

*All radioimmune assays for AFP and B-HCG were performed by Dr. Thomas Waldmann, National Institute of Health, Bethesda, Maryland.
†Kallestad Laboratories, Chaska, Minnesota.

The results as presented in Table 2 demonstrate that the radioimmune assay method for determining serum AFP levels is much more sensitive than the conventional gel-agar precipitation method. For example, of the 15 sera tested both by gel-agar precipitation and radioimmune assay methods, ten had elevated AFP values by radioimmune assay, whereas only three were positive by the conventional method.

The Figure demonstrates that an elevated level of either AFP, B-HCG, or both in the sera has a high correlation with the presence of active non-seminomatous germ cell testicular tumor. In only one of 13 cases was there clinical evidence of the disease and yet no elevation of either serum marker. In one patient, an elevated AFP was found but he remains clinically free of disease and is currently under close observation.

CORRELATION OF AFP AND B-HCG WITH ACTIVE DISEASE

	AFP +	AFP −
Active +	11	2
Disease −	1*	8

	AFP +/or h'CG +	AFP +/or h'CG −
Active +	12	1
Disease −	1	8

*Under Close Observation

Figure

Discussion

Alpha-fetoprotein is a 70,000 molecular weight protein of alpha 1 electrophoretic mobility which is synthesized by the liver, yolk sac, and gastrointestinal tract of the mammalian fetus. It is readily detectable by conventional methods in human fetal sera, but after one year of age it is not detectable in sera by gel-agar precipitation, methods (including the immunoelectro-osmophoresis method) which have sensitivity levels between 1,000 and 3,000 ng per ml. However radioimmune assay techniques can detect low serum levels of AFP which, in a normal person after one year of age, are always less than 40 ng per ml.[2]

Before a radioimmune assay became available, detectable levels of AFP were found in adults with primary hepatocellular cancers (approximately 70 percent).[7] Using these early methods, investigators also found serum AFP in 15 to 50 percent

of patients with teratocarcinoma of the testicle and ovary.[4] However when similar patients were studied using radioimmune assay techniques, elevated AFP levels were found in 70 percent of patients with teratocarcinoma or embryonal cell carcinoma of the testis, in about 70 percent of patients with hepatomas, and to a lesser degree in patients with pancreatic, gastric, colonic, or bronchogenic cancer. Thus, the more sensitive radioimmune assays for AFP have shown AFP to be elevated almost as frequently in patients with nonseminomatous germ cell cancers of the testicle as in patients with hepatomas. This increased association of AFP with testicular tumor is due to the fact that patients with nonseminomatous germ cell tumors rarely have AFP levels greater than 3,000 ng per ml., which is the lower limit of sensitivity for many of the gel-agar precipitation methods currently available; whereas patients with hepatomas often develop levels above 3,000 ng per ml. Our data illustrate the increased sensitivity of radioimmune assay for AFP in that the serum of only three of ten testicular tumor patients with elevated AFP values by radioimmune assay had detectable AFP by a conventional method.

In this series of patients the serum level of B-HCG was elevated in 46 percent of patients (six of 13) with active non-seminomatous testicular tumors. However AFP was elevated in 80 percent of patients with active disease and AFP, B-HCG, or both were elevated in 85 percent of active cases. Thus, AFP and B-HCG seem to be reliable indicators of at least widespread disease, and may be useful in assessing the adequacy of treatment designed to cure the patient, such as radical retroperitoneal lymph node dissection[8] combined with adjuvant therapy (chemotherapy, or radiation, or both). As a matter of fact, some investigators have suggested that serial determinations of serum AFP and B-HCG can be useful as a guide to chemotherapy in patients with either persistent or recurrent disease, but the number of observations are few and the results are anecdotal.[4,9,10]

Moreover, it is clear from our recent experience with these markers that in patients who have apparently had all their disease removed by surgery, a subsequent rise in serum levels of AFP, B-HCG, or both often precedes the development of recurrent tumor. Thus these marker proteins in the serum may indicate the presence of disease at a time when the tumor is too small to be detected by other means. If further experience substantiates that rises in serum levels of these markers almost always indicate active disease, it may be possible to increase the number of cancer cures in these patients by applying conventional therapy earlier or introducing new modes of therapy such as immunotherapy.

Whether the AFP or B-HCG assays would be useful in the differential diagnosis of scrotal masses or as screening tests to detect small occult tumors located in the testes is not known because almost no studies have been carried out in patients with the primary tumor still in place. It would seem that determination of serum AFP and B-HCG might be indicated in patients at high risk to develop testicular cancers such as: (1) patients with an undescended testicle, (2) an identical twin whose other twin had a testicular tumor, and (3) patients who have been "cured" of their disease since second primary tumors are not uncommon in testicular cancer.

Presently we are studying the correlation of B-HCG and AFP levels in patients with all stages of testicular tumor. Preliminary indications including those given above suggest that these tests may be very sensitive indicators for the presence of malignant, non-seminomatous germ cell tumors of the testicle. If further experience confirms these findings, the measurement of serum levels of AFP and B-HCG will expand the possibilities for improved modes of diagnosis and therapy in certain patients with testicular tumors.

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Alcoholic Hepatitis

WILLIAM J. MARTIN, II, M.D.* AND JAMES J. GARBER, M.D.†

Three cases of alcoholic hepatitis diagnosed by liver biopsy are presented. The presence of neutrophilic infiltration, hepatocyte necrosis and Mallory bodies were required for diagnosis. The three cases represent a spectrum of clinical presentations of this entity. The historical, pathological and clinical significance of the Mallory body is discussed and clinical features of alcoholic hepatitis reviewed.

In 1911, MALLORY DESCRIBED a particular histologic finding in alcoholic liver disease which still bears his name. This "irregular, coarse hyaline meshwork" found in degenerating liver parenchymal cells was thought by Mallory to be associated exclusively with liver change secondary to the ingestion of alcohol.[1] The Mallory body has become one of the common pathologic criteria used for the diagnosis of acute alcoholic hepatitis.[2] Two other features commonly sought in making this diagnosis are cellular necrosis and infiltrating polymorphonuclear cells.[2,3] It is this triad of cellular necrosis, polymorphonuclear infiltration and hyaline degeneration that has been used in this study to establish the diagnosis of acute alcoholic hepatitis.

Materials and Methods

All cases admitted to the Olmsted Community Hospital, Rochester, Minnesota from 1967 to 1973 were reviewed for evidence of alcoholic hepatitis. Three cases were found which showed evidence of alcoholic hyaline, as well as neutrophilic infiltration and cellular necrosis of the liver. These represent the basis for this paper.

Case Reports

Case 1

A 31-year-old woman was admitted to the Olmsted Community Hospital on November 25, 1968 with a three or four day history of nausea and vomiting. One year before she had been seen elsewhere for abdominal complaints. No studies had been done at that time and she was treated with some type of suppository. In July of 1968 she was seen at the Olmsted Medical Group for generalized abdominal pain which came on abruptly four days prior to her visit. At that time an upper gastrointestinal series was performed and showed only minimal duodenal irritability. Five or six days prior to admission she noted recurrent generalized abdominal discomfort followed by the onset of diarrhea the following day. Vomiting described as green and yellow bile had also occurred.

On physical examination, the patient was noted to be pale, cold, dyspneic, and acutely ill. The sclerae were icteric. A grade I/VI apical systolic ejection murmur was heard on examination of the heart. The pulse was 120. The lungs were clear. The abdomen was noted to be distended and generally tender. There was massive enlargement of the liver essentially filling the entire abdomen to the pubis. No spleen or other masses were noted. Pelvic examination was essentially negative. The ankle jerks were absent. The patient's temperature was 101.4 F.

Laboratory studies included a white blood cell count of 30,800 cells per cubic mm. There were 88 neutrophils, four stabs, three lymphocytes, two juvenile forms, one monocyte and one eosinophil. The hemoglobin was 7.2 grams %. Sedimentation rate was 100 mm/hr., blood urea nitrogen 5 mg.%, sodium 132 mEq/liter, potassium 2.8 mEq/liter, fasting blood sugar 95 mg.%. The urinalysis included a specific gravity of 1.025 with negative albumin, 2+ glycosuria, negative acetone, rare white and red blood cells and a large amount of bile. The serum iron was 136 mcg.%, mean corpuscular hemoglobin 29 mcg.%, mean corpuscular hemoglobin concentration 31%, mean corpuscular volume 95 cubic mcg. Reticulocyte count was 0.8%, prothrombin time was 16 seconds with a control of 13, thymol turbidity 13.8, transaminase 600 International units, uric acid 3.5%, serum bilirubin, direct 2.19 mg.%, indirect 2.53 mg.%, with a total of 4.72 mg.%. Stool for Guaiac was 2+. Chest Xray and flat plate of the abdomen were negative.

One blood culture grew out a few bacillis species, though a second culture was sterile. Stool culture showed no pathogens. Repeat white blood cell count was 50,800 with 82 neutrophils, three stabs, and nine lymphocytes. Subsequently, the white blood cell count fell to 10,300 with 65 neutrophils, five stabs, and 21 lymphocytes. Her hemoglobin fell to 6.5 grams. A Coombs' test was nega-

*Resident, Internal Medicine, Mayo Graduate School of Medicine, Rochester.
†Internist, Olmsted Medical and Surgical Group, P. A. Rochester, Minnesota.
See editorial, page 827.

tive, the lactic dehydrogenase was 120 International Units, amylase under 100 Smogyi units and a repeat transaminase 148 International units. The serum bilirubin rose to a total of 10.64 mg.%. Proctoscopic examination was negative to 10 cm.

During the patient's hospital course, she showed a gradual deterioration, was incontinent, and became unresponsive. Her temperature rose to a maximum of 105.4°F. The patient continued to vomit during the course of her hospital stay and the abdominal pain persisted. The patient was placed on Cephlathin 0.5 grams every four hours and Cholemycin 50 mg. every six hours. Subsequently, a history was obtained from the patient's relatives of a heavy alcoholic intake as well as previous psychiatric therapy for drug habituation. The extent of her alcohol ingestion and the type of drug habituation were not determined. The patient expired on the second hospital day.

Postmortem examination revealed pulmonary edema with a total lung weight of 1525 grams and marked hepatomegaly (weight 4120 grams). There was marked fatty infiltration of the liver with early cirrhosis. Microscopic examination revealed numerous polymorphonuclear leukocytes, lymphocytes and an occasional eosinophil. Alcoholic hyaline was seen in some of the more normal parenchymal cells. Regenerative nodules were noted. Other postmortem findings included a septic appearing spleen with splenomegaly (weight 410 grams), minimal healed focal pyelonephritis involving both kidneys, lipid depletion adrenals, and atherosclerosis of the aorta, grade I and of the coronary arteries, grade I.

Case 2

A 35-year-old man was admitted to the Olmsted Community Hospital on November 30, 1970 with a six month history of pain in the back of the neck. The patient had noted three previous episodes of sharp, posterior neck pain associated with syncope lasting approximately ten minutes. The last such episode had occurred one and one-half months prior to admission. Observers at the time of these episodes denied any evidence of a seizure disorder. The patient had also been aware of anorexia and a 12 pound weight loss during the past six months. He noted easy filling, constipation and had several episodes of "coffee ground" emesis occurring almost weekly for the past six months. He admitted to drinking six to eight bottles of beer per day. Three weeks prior to admission, the patient developed a "chest cold" and on admission, continued to have a cough productive of white to yellow sputum.

Past medical history was unremarkable. The patient was adopted and no family history was obtainable. The patient admitted to smoking one to one and a half packs of cigarettes per day. Review of systems was essentially negative.

On physical examination, the patient was noted to be pale, and coughing frequently. Pertinent physical findings included tachycardia of 136, hepatonegaly with the liver extending ten cm. below the right costal margin. The liver was non-tender and smooth. There was a small left inguinal hernia.

Laboratory studies included a hemoglobin of 4.5 grams %, hematocrit 19%, sedimentation rate 138. Special examination of the peripheral blood forms revealed a marked anisocytosis with some hypochromasia, oval macrocytes and hypersegmented white blood cells. The urinalysis revealed a specific gravity of 1.015. There was no albumin, sugar, acetone or bile present. There were two to three white blood cells per high power field. The other laboratory studies included a total thyroxine of 5.0 mg.%, bromsulphthaline dye retention of 6% in one hour, serum bilirubin, direct 0.5, indirect 0.5 with a total of 1.0, alkaline phosphatase 86 International units, transaminase 37 International units, thymol turbidity 1 unit, serum iron 219 mg.% iron binding capacity 261 mg.%. The white blood cell count was initially 12,000 with 76 neutrophils, one stab, two lymphocytes, two eosinophils, one basophil, five monocytes. Serum protein electrophoresis was normal. The uric acid was 6.2 mg.%, cholesterol 145 mg.%, calcium 8.0 mg.%, triglycerides 98 mg.%, blood urea nitrogen 13.4 mg.%, lactic dehydrogenase 122 International Units, Coombs' negative, platelets 610,000, prothrombin time 13 with a control of 13, partial thromboplastin time of 30 seconds and a gastric analysis showed free acid. Urine, sputum and blood cultures were sterile. Serum B-12 was 1050 picograms per ml. and the serum folic acid was 0.6 nanograms per ml. Reticulocyte count was 2%, stool for Guaiac was negative, chest Xray showed a Ghon comples, colon and upper gastrointestinal series were normal. Subsequently, the white blood cell count rose to 22,500 with a differential count showing 91 neutrophils and one stab and eight lymphocytes.

During the hospital course, the patient had no episodes of neck pain or syncope. He was placed on folic acid and given one injection of vitamin B-12. His hemoglobin rose to a high of 9.5 grams % at the time of dismissal. During the course of his hospital stay, a liver biopsy was performed which showed evidence of moderate fatty metamorphosis, fibrosis, marked infiltration of neutrophils, some necrosis and alcoholic hyaline. The patient generally improved and was dismissed after a program, designed to treat his chronic alcoholism, was agreed upon by the patient and his wife.

Case 3

A 50-year-old white male was admitted on July 14, 1971 for alcoholic detoxification. The patient had a known history of an excessive alcoholic intake since World War II. In the past four years, the problem had been more prominent. Over the past one month, the patient had been drinking steadily. He admitted to taking approximately one pint of whiskey per day. The patient had had previous exposures to Alcoholics Anonymous and other alcoholic treatment programs including one hospitalization elsewhere for detoxification two years previously.

Family history revealed that a sister had died of cirrhosis of the liver and alcoholism. The patient was a bachelor. In the past, the patient had had alcoholic gastritis and associated upper gastrointestinal bleeding.

Physical examination revealed a moderately depressed

white male who was tremulous. There were scattered spider telangiectasis as well as hyperemia of the palms and soles. On examination of the abdomen, the liver was noted to extend six to eight cm. below the right costal margin. The liver edge was quite firm to hard and minimally tender. No spleen was palpable. Deep tendon reflexes were reduced at the knees and absent at the ankles.

Laboratory studies included a hemoglobin of 16 grams %, hematocrit 46%, white blood cell count of 8350 with 73 neutrophils, 26 lymphocytes and one monocyte. Urinalysis showed a specific gravity of 1.017 with one to three white blood cells per high power field. The sedimentation rate was 49 mm/hr. Fasting blood sugar was 275 mg.% and subsequently 145 mg.%, BUN 16, uric acid 6.1 mg.%, calcium 9.1 mg.%, cholesterol 280 mg.%, triglycerides 73 mg.%. Total thyroxine was 3.3 micrograms %, transaminase 117 International units, alkaline phosphatase 64 International units, lactic dehydrogenase 215 International units, bromsulphthaline dye retention was 11% in one hour, thymol turbidity 5.3 units, VDRL negative, prothrombin time 13 seconds with a control of 13 seconds, partial thromboplastin time 38 seconds with a control of 37 seconds, and a platelet count of 137,000. Serum potassium was 4.3 mg.%. A repeat transaminase was 172 International units, and the alkaline phosphatase 77 International units. The chest Xray and upper gastrointestinal series were normal. An intravenous pyelogram reveals the right kidney to be 12 cm. and the left kidney to be 14 cm. No lesions were seen. Electrocardiogram showed a sinus tachycardia of 120 per minute. A liver biopsy revealed some increase in fibrous tissue with about 10% replacement by intracytoplasmic fat globules. The hepatocytes showed some degeneration with alcoholic hyaline. There were some necrotic cells with infiltration of neutrophils. The patient was afebrile on admission and remained so during the course of his hospitalization. His tremulousness gradually cleared and the patient was subsequently referred to a primary treatment center for chronic alcoholism.

Discussion

The clinical features seen in alcoholic hepatitis are in general, non-specific and of little aid in predicting the underlying liver pathology. The classical clinical presentation of a patient with acute alcoholic hepatitis includes complaints of anorexia, weight loss, weakness, abdominal pain and a history of alcohol overuse. Physical findings may reveal tender hepatomegaly, jaundice and fever which in these patients are often associated with signs of chronic liver disease, i.e. splenomegaly, ascites, edema, increase in venous collaterals on the abdominal wall, gynecomastia, peripheral neuropathy, spider nevi, palmer erythema and Dupuytren's contractures. Laboratory data correlates well with the clinical presentation revealing anemia, leucocytosis with a shift to the left, elevated serum glutamic oxalacetic transaminase, alkaline phosphatase, and bilirubin; prolonged prothrombin time, decrease in albumin-globulin ratio and bromsulphthalein dye retention.[2,3,4]

It is of importance to stress that the disease is of acute onset and varies greatly in its severity. The three patients included in this study represent the broad spectrum of symptoms commonly encountered in acute alcoholic hepatitis. Clinically, the features of this disease are those of a non-specific hepatitis, and reflect the sudden and often serious compromise of liver function. Mallory bodies, as described in 1911, are found in degenerating liver parenchymal cells.[1] Under the light microscope, they appear as refractile, eosinophilic, irregular masses which tend to coalesce and are usually perinuclear in location.[5] Under the electron microscope, the hyaline mass appears as an aggregation of fibrils which is not enclosed within a membrane.[6] This characteristic allows one to sufficiently distinguish the Mallory body from intracellular organelles such as megamitochondria. The biochemical constituents of the Mallory body are those of a lipoprotein complex which has been shown to be paramino acid Schniff negative indicating a lack of carbohydrate.[5,7] It is possible to characterize the Mallory body on the basis of morphology under the light and electron microscope and in addition, to characterize it biochemically as a lipoprotein complex.

The prognosis of those patients who had pathologic evidence of Mallory bodies was at one time thought to be exceedingly poor.[8,9] However, more recent studies place the mortality rate of patients with Mallory bodies under 20%.[2,3,4,10] Harinasuta et al.[4] found no significant difference in mortality in those patients who had the same clinical features with or without the Mallory bodies. Thus it would seem that the mortality associated with hyaline degeneration simply reflects the serious damage to the liver parenchymal cells which is seen generally in alcoholic liver disease and is not the result of any specific association with the Mallory body.

The term "acute alcoholic hepatitis" was first used by Beckett et al.[11] to describe the alcoholic patient who presented with the clinical features of jaundice, anorexia, nausea, vomiting, upper abdominal pain, hepatomegaly and fever. The his-

tologic findings were typical of those found in hepatitis, i.e. hepatocellular necrosis and inflammation. The Mallory body was often present, but was not required for diagnosis. The necessity for the presence of alcoholic hyaline has not been settled, as evidenced by the divergence of recent authors regarding its use as a necessary pathologic criterion. The high correlation of the presence of alcoholic hyaline with the chronic ingestion of alcohol has prompted us to include this pathologic feature in the diagnostic triad of acute alcoholic hepatitis. The other two pathologic criteria, i.e. hepatocellular necrosis and infiltrating polymorphonuclear cells indicate the inflammatory reaction of the liver seen in all hepatitides regardless of the etiology.

The Mallory body has been found in other disease states such as primary hepatoma,[7,12] ulcerative colitis,[13] Wilson's disease,[14] and infantile cirrhosis of India.[15] It is necessary, therefore, when encountering the Mallory body in a biopsy specimen to include the above disease states in the differential diagnosis. However, the relative rarity of the Mallory body in patients without a history of alcoholism allows one to utilize this pathologic feature, in the practical sense, as being exclusive of nonalcoholic disease. The reason for the association of the excessive intake of alcohol with this particular type of hyaline degeneration is unknown, but remains an intriguing question in the pathology of the liver.[16]

The clinical spectrum of acute alcoholic hepatitis, regardless of the underlying liver pathology, is nonspecific, and cannot be differentiated from other alcoholic liver diseases on a clinical basis. The three cases presented in this article manifest well the broad spectrum of symptoms and severity of the clinical disease, one with mild symptoms, another with moderate clinical symptoms of liver disease and a third a mortality. It also serves to emphasize the value of the recommendation of Green et al.[3] that the diagnosis of acute alcoholic hepatitis should be reserved for chronic alcoholics who present with a history of drinking up to the time of hospital admission. The disease usually manifests itself as an acute exacerbation of an already seriously compromised liver. The presentation of these three cases in a small community hospital exhibits clearly that while acute alcoholic hepatitis is not the most common manifestation of alcoholic liver disease, it is by no means rare. Its recognition as a definitive pathologic entity within the spectrum of alcoholic liver disease is possible and helpful in differential diagnosis of hepatitis or nonalcoholic origin.

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Minnesota Urological Society

Minnesota Urological Society will meet at L'hotel Sofitel on Friday, November 21, for the purpose of conducting Pyelogram Conferences. Contact: William E. Price, M.D., Secretary, Metropolitan Medical Building, Minneapolis 55404.

Chorioangioma of the Placenta

Causing Fetal Distress

JOSEPH E. ADDUCCI, M.D.*

A case is presented of giant chorioangioma of the placenta occurring and diagnosed as a problem of fetal distress. The presentation emphasizes the need for fetal cardiac monitoring of all labors including those without ante partum complications.

THIS PAPER DOCUMENTS the case of giant chorioangioma of the placenta in close proximity to the umbilical cord insertion with concomitant fetal distress in labor.

Chorioangioma of the placenta is an uncommon complication of pregnancy, ranging in frequency from one in a hundred cases of small, minute tumors, to one in 20,000 for the giant tumor variation. Most of these tumors are surrounded by layers of syncytium with variable amounts of fibrous degeneration. Major and minor degrees of calcification and infarction may also be present. The tumor mass consists predominantly of proliferating endothelial cells with varying degree of vascular proliferation. These tumors are entirely benign. Electron microscopy revealing normal karyotype, as opposed to the usual bizarre patterns of karyotype demonstrated in malignant lesions.[4]

Many and varied complications have been reported in association with chorioangiomata.[2] These would include toxemia of pregnancy, with concomitant problems of abruption, post-partum bleeding, polyhydramnios, skin hemangiomata, nevi on the baby, as well as, other congenital malformations have been present.[1] Since this tumor actually represents an arterial venous fistula for the baby, cardiomegaly and congestive heart disease have been reported.[3,5]

*Department of Obstetrics, Mercy Hospital, Williston, North Dakota, UND Medical School.

See editorial, page 827.

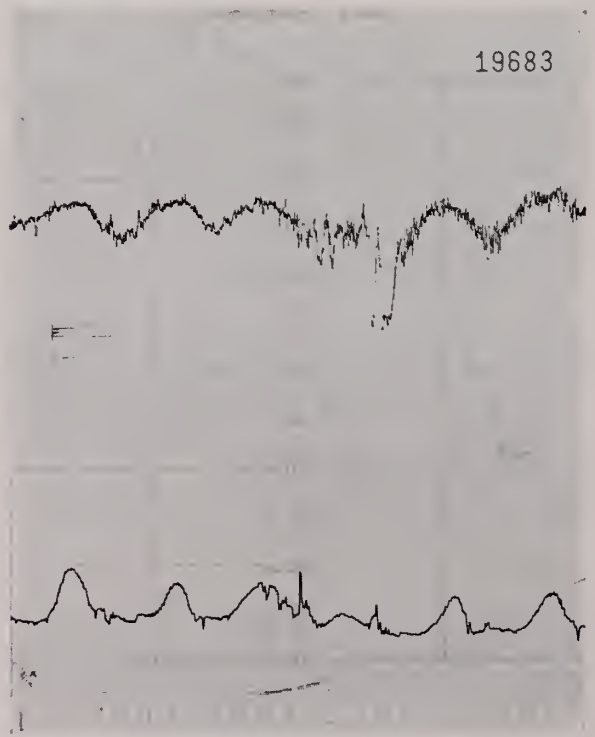


Fig. 1—Fetal ECG pattern before oxytocin challenge.

Case Report

A twenty-one year old, Para I, Gravida O, white female entered the hospital with prodromal labor. She was about one week beyond her expected date of delivery. Fetal monitoring was begun, although labor was never of good quality. During the course of the evening, a few delayed deceleration patterns were demonstrated and by early morning, all labor had ceased. An oxytocin challenge was given the following morning, with a drop of the fetal heart rate to 70. The patient was then taken immediately to the operating room, where a low, transverse cervical Caesarean Section was performed. A living female infant was delivered. Birth weight was 3790 gm., 54 cm. in length. The placenta demonstrated a giant chorioangioma, location within two cm. of the cord insertion. The tumor measured 6.1 x 4.7 x 4.7 cm. with microscopic necrosis at the periphery, the remainder

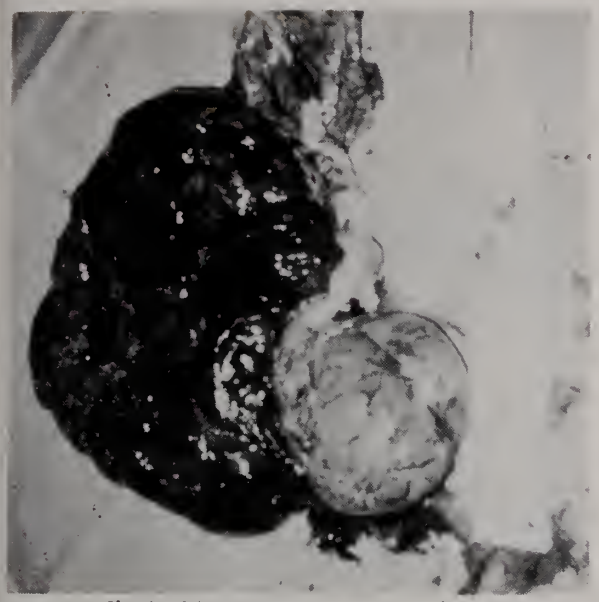


Fig. 2—Placenta and tumor at delivery.

of the placenta demonstrating a normal histologic structure.

The baby was entirely normal after resuscitation; Apgar 5 at one minute and Apgar 9 at three minutes. The baby, on examination, showed no evidence of any malformation, nor evidence of congestive heart failure. Both mother and baby did well and were discharged on the seventh postoperative day.

Summary

This paper reports a twenty-one year old woman who had a chorioangioma of the placenta and required a Caesarean section for delivery of a live infant. The case underscores the necessity of fetal cardiac monitoring and the usefulness of oxytocin challenge test in managing pregnancy without complications.

This placental tumor, although not of a malignant nature, has the potential of lethal complications regarding the fetus, but because of its rarity, has not been significantly considered as a major factor in labor. The concomitant fetal postpartum abnormalities possible, must be immediately evaluated and coped with to prevent morbidity.

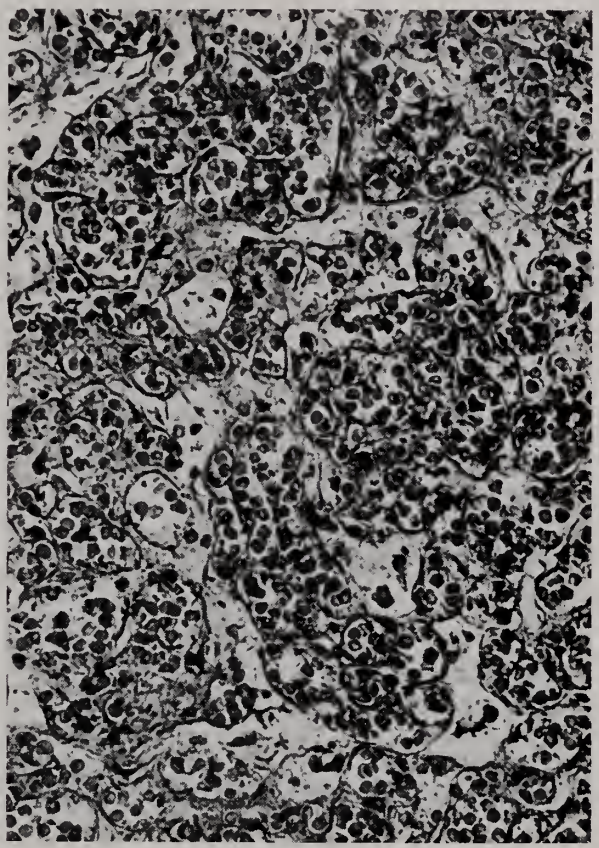


Fig. 3—Photomicrograph of tumor H. E. stain 160 x mag.

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Letters to the Editor

We would like to encourage physicians to contribute to the Letters to the Editor Section. We want to hear what you have to say, what you think, why you hold certain opinions. In short, we want to make this as lively and spirited a section as possible.

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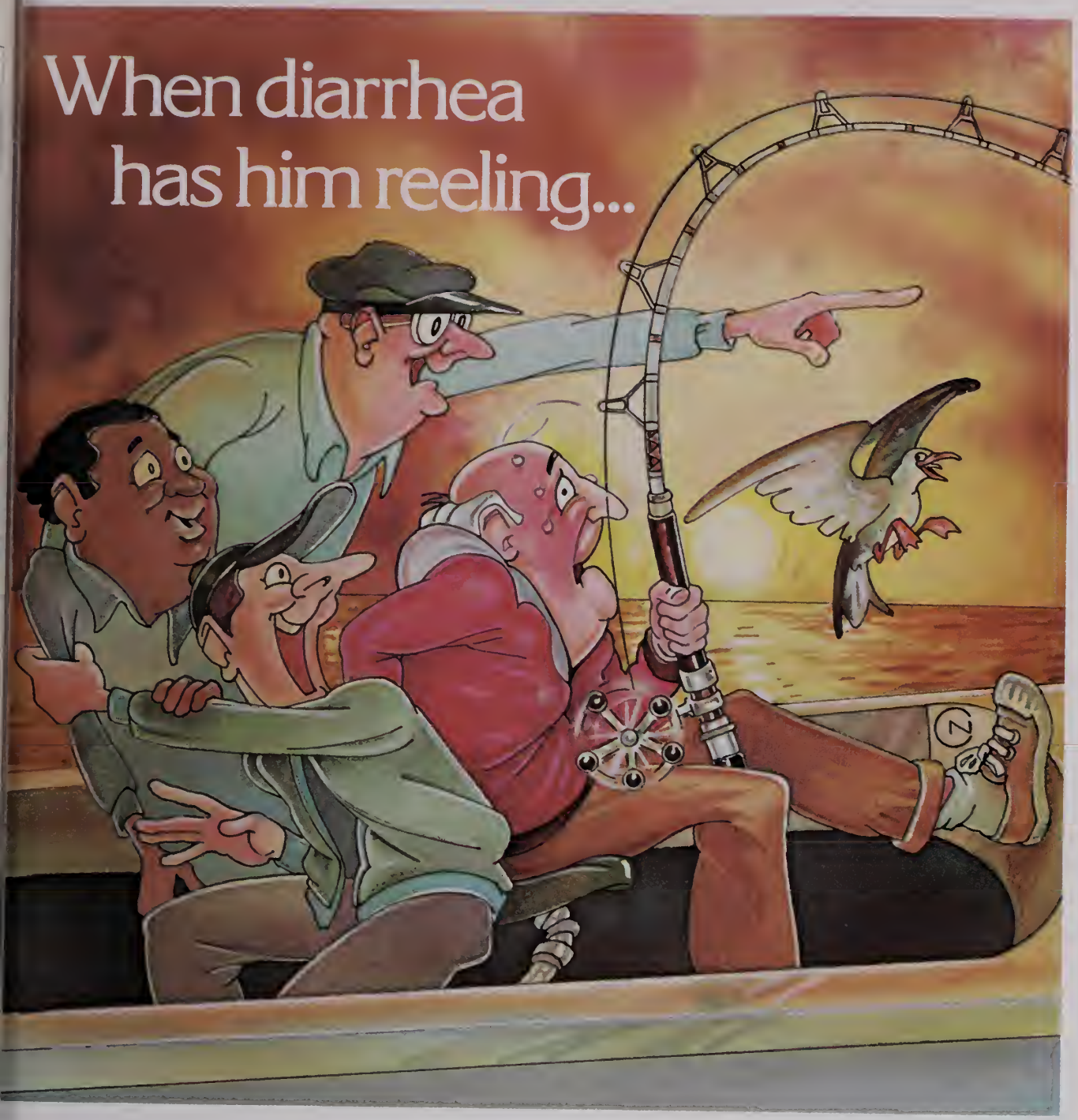
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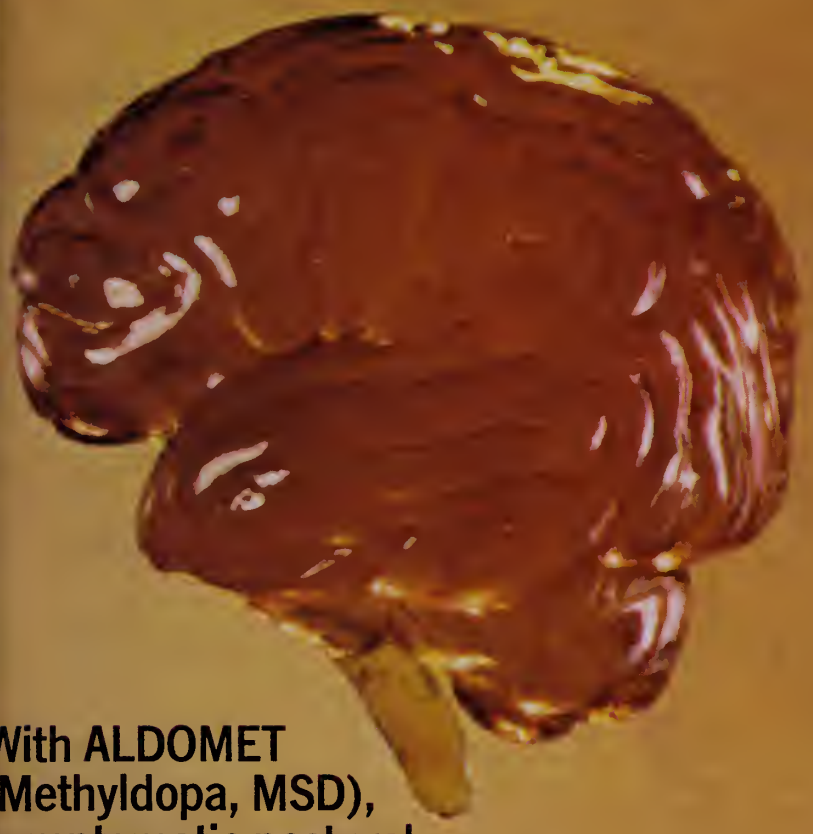


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addendum

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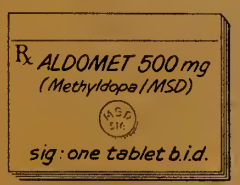
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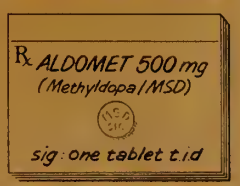
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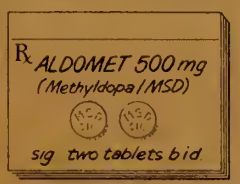
1.0-g daily dose =

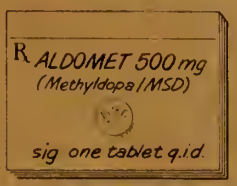


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Contraindications: Active hepatic disease, such as acute hepatitis and active cirrhosis; if previous methyldopa therapy has been associated with liver disorders (see Warnings); hypersensitivity.

Warnings: It is important to recognize that a positive Coombs test, hemolytic anemia, and liver disorders may occur with methyldopa therapy. The rare occurrences of hemolytic anemia or liver disorders could lead to potentially fatal complications unless properly recognized and managed. Read this section carefully to understand these reactions.

With prolonged methyldopa therapy, 10% to 20% of patients develop a positive direct Coombs test, usually between 6 and 12 months of therapy. Lowest incidence is at daily dosage of 1 g or less. This on rare occasions may be associated with hemolytic anemia, which could lead to potentially fatal complications. One cannot predict which patients with a positive direct Coombs test may develop hemolytic anemia. Prior existence or development of a positive direct Coombs test is not in itself a contraindication to use of methyldopa. If a positive Coombs test develops during methyldopa therapy, determine whether hemolytic anemia exists and whether the positive Coombs test may be a problem. For example, in addition to a positive direct Coombs test there is less often a positive indirect Coombs test which may interfere with cross matching of blood.

At the start of methyldopa therapy, it is desirable to do a blood count (hematocrit, hemoglobin, or red cell count) for a baseline or to establish whether there is anemia. Periodic blood counts should be done during therapy to detect hemolytic anemia. It may be useful to do a direct Coombs test before therapy and at 6 and 12 months after the start of therapy. If Coombs-positive hemolytic anemia occurs, the cause may be methyldopa and the drug should be discontinued. Usually the anemia remits promptly. If not, corticosteroids may be given and other causes of anemia should be considered. If the hemolytic anemia is related to methyldopa, the drug should not be reinstituted. When methyldopa causes Coombs positivity alone or with hemolytic anemia, the red cell is usually coated with gamma globulin of the IgG (gamma G) class only. The positive Coombs test may not revert to normal until weeks to months after methyldopa is stopped.

Should the need for transfusion arise in a patient receiving methyldopa, both a direct and an indirect Coombs test should be performed on his blood. In the absence of hemolytic anemia, usually only the direct Coombs test will be positive. A positive direct Coombs test alone will not interfere with typing or cross matching. If the indirect Coombs test is also positive, problems may arise in the major cross match and the assistance of a hematologist or transfusion expert will be needed.

Fever has occurred within first 3 weeks of therapy, sometimes with eosinophilia or abnormalities in liver function tests, such as serum alkaline phosphatase, serum transaminases (SGOT, SGPT), bilirubin, cephalin cholesterol flocculation, prothrombin time, and bromsulphalein retention. Jaundice, with or without fever, may occur, with onset usually in the first 2 to 3 months of therapy. In some patients the findings are consistent with those of cholestasis. Rarely fatal hepatic necrosis has been reported. These hepatic changes may represent hypersensitivity reactions; periodic determination of hepatic function should be done particularly during the first 6 to 12 weeks of therapy or whenever an unexplained fever occurs. If fever and abnormalities in liver function tests or jaundice appear, stop therapy with methyldopa. If caused by methyldopa, the temperature and abnormalities in liver function characteristically have reverted to normal when the drug was discontinued. Methyldopa should not be reinstituted in such patients.

Rarely, a reversible reduction of the white blood cell count with primary effect on granulocytes has been seen. Reversible thrombocytopenia has occurred rarely. When used with other antihypertensive drugs, potentiation of antihypertensive effect may occur. Patients should be followed carefully to detect side reactions or unusual manifestations of drug idiosyncrasy.

Use in Pregnancy: Use of any drug in women who are or may become pregnant requires that anticipated benefits be weighed against possible risks; possibility of fetal injury can not be excluded.

Precautions: Should be used with caution in patients with history of previous liver disease or dysfunction (see Warnings). May interfere with measurement of: uric acid by the phosphotungstate method, creatinine by the alkaline picrate method, and SGOT by colorimetric methods. Since methyldopa causes fluorescence in urine samples at the same wavelengths as catecholamines, falsely high levels of urinary catecholamines may be reported. This will interfere with the diagnosis of pheochromocytoma. It is important to recognize this phenomenon before a patient with a possible pheochromocytoma is subjected to surgery. Methyldopa is not recommended for patients with pheochromocytoma. Urine exposed to air after voiding may darken because of breakdown of methyldopa or its metabolites.

Stop drug if involuntary choreoathetotic movemen occur in patients with severe bilateral cerebrovasc lar disease. Patients may require reduced doses anesthetics; hypotension occurring during ane thesia usually can be controlled with vasopressor Hypertension has recurred after dialysis in patien on methyldopa because the drug is removed by th procedure.

Adverse Reactions: *Central nervous syste* Sedation, headache, asthenia or weakness, usua early and transient; dizziness, lightheadednes symptoms of cerebrovascular insufficienc paresthesias, parkinsonism, Bell's palsy, decreas mental acuity, involuntary choreoathetotic mov ments; psychic disturbances, including nightmar and reversible mild psychoses or depression.

Cardiovascular: Bradycardia, aggravation of angi pectoris. Orthostatic hypotension (decrease da dosage). Edema (and weight gain) usually relieve by use of a diuretic. (Discontinue methyldopa edema progresses or signs of heart failure appea

Gastrointestinal: Nausea, vomiting, distention, co stipation, flatus, diarrhea, mild dryness of mouth, so or "black" tongue, pancreatitis, sialadenitis.

Hepatic: Abnormal liver function tests, jaundic liver disorders.

Hematologic: Positive Coombs test, hemolyt anemia. Leukopenia, granulocytopenia, thror bocytopenia.

Allergic: Drug-related fever, myocarditis.

Other: Nasal stuffiness, rise in BUN, breast enlarg ment, gynecomastia, lactation, impotence, decreas libido, dermatologic reactions including eczema a lichenoid eruptions, mild arthralgia, myalgia.

Note: Initial adult dosage should be limited 500 mg daily when given with antihypertensiv other than thiazides. Tolerance may occur, usua between second and third month of therapy; i creased dosage or adding a thiazide frequent restores effective control. Patients with impair renal function may respond to smaller doses. Sy cope in older patients may be related to increas sensitivity and advanced arteriosclerotic vascul disease; this may be avoided by lower doses.

How Supplied: Tablets, containing 125 m methyldopa each, in bottles of 100; Tablets, conta ing 250 mg methyldopa each, in single-un packages of 100 and bottles of 100 and 100 Tablets, containing 500 mg methyldopa each, single-unit packages of 100 and bottles of 100.

For more detailed information, consult your MS representative or see full prescribing inform tion. Merck Sharp & Dohme, Division of Merck Co., Inc., West Point, Pa. 19486

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Editorials

Alcoholic Hepatitis

MARTIN AND GARBER'S* informative review of alcoholic hepatitis again brings into focus one of the protean physical manifestations of chronic alcohol abuse. The authors correctly conclude that the clinical picture of this pathologic entity is highly variable, and that the diagnosis is established only by liver biopsy; the severity of the acute inflammatory changes in the liver and of the degree of overt hepatocellular necrosis do, however, appear to correlate with the patient's clinical appearance at the time of biopsy.

The treatment of this potentially catastrophic disease deserves some mention. During the acute phase of the illness, supportive measures are certainly in order; various more specific therapeutic regimens including the use of high doses of corticosteroids have failed to prove efficacious. The only factor which has been demonstrated to be of benefit is maintenance of abstinence from alcohol. Utilization of an alcoholic treatment center provides the practicing physician with his most potent weapon in the management of this complication of acute and chronic alcoholism.

Todd C. Miller, M.D.
Minneapolis, Minneota

*See page 816.

Importance of Fetal Heart Rate Monitoring

DR. JOSEPH ADDUCCI presents a case report* of fetal distress apparently secondary to a giant chorioangioma of the placenta. No other antepartum or intrapartum complications were present. Routine fetal heart rate auscultation may have missed this abnormality with resultant mortality or morbidity. Possibly this rare anomaly may cause a late deceleration pattern secondary to decreased placental function or a variable deceleration pattern from umbilical cord compression. In addition, baseline variability of the fetal heart rate is an important criterion of fetal cardiac reserve.

Although this rare condition is interesting, the emphasis of the article is on total fetal heart rate monitoring of all labors. Unfortunately, this is not feasible in most labor suites. Monitoring should be done, however, when there is any other evidence of fetal distress or when the fetus is suspected of being compromised by other coexisting conditions. The induction or stimulation of labor with pitocin is another indication for monitoring. Thus by adequate fetal montoring we can hope to reduce even more the perinatal mortality and morbidity.

William C. Meyer, M.D.
Edina, Minnesota

*See page 820.

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Streptococcal Control in School Children

THE ARTICLE BY Phibbs* in the August issue presents the mechanics, goals and results of a school streptococcal surveillance program in a heavily endemic county of Wyoming. Despite excellent documentation of his results, and the results of others in such programs, several questions need to be raised.

The use of throat cultures in children whose only symptom is sore throat is less accurate than when fever and sore throat are used as combined criteria for throat culture.[1] In this study, the decreased incidence of streptococcal infection may have been related to the reduced streptococcal carrier state because those children, who were clinically ill, might well have remained at home and not been cultured. Also, student reporting of sore throat or cold symptoms, as well as evaluating pharyngeal inflammation in asymptomatic students, are both subjective and could strongly contribute to reduction of the carrier state. Reduction of the carrier state may be desirable, but at the present time there is no definitive evidence that treatment of the carrier state alone has a significant effect on the reduction of the sequelae of streptococcal infection.

The main benefit of such a program, as pointed out by Phibbs, is the educational approach to the various aspects of streptococcal disease, both for the public and the medical profession. The ease of overutilization, as previously discussed, would seem to be the greatest potential disadvantage. The article omits any discussion of possible convenience or economy of this program to the families. Any final evaluation of the program must assess the benefits of economy and convenience relative to possible overutilization problems. The ultimate goal of such a program, i. e., the reduction of the sequelae of streptococcal disease, cannot and should not be challenged. Caution should be exercised so that strict prospective evaluation over an adequate period of time will insure that the ultimate goal can be attained.

Phillip A. Rierson, M.D.†
Minneapolis, Minnesota

*Phibbs BP: Streptococcal control in school children. Minnesota Med 58:607, 1975.
†Posthumous.

Reference

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Management of Tibial Fractures

THE RECENT ARTICLE by Kennedy, Premer and Lagaard* shows the advantages of the conservative functional treatment of tibial shaft fractures. Minimal morbidity and rapid rehabilitation can be achieved in the vast majority of cases by the method popularized by Sarmiento. Using this method in over 100 winter sports tibial fractures abroad, I have seen no serious complications. We tended to apply the PTB cast earlier, often within the first two weeks and allowed full weight bearing as soon as tolerated. The very few instances of delayed unions were treated with decortications (Judet).

Essentially, I agree with the authors' management of compound fractures. However, in type II wounds, I prefer to delay the wound closure four to six days.

In severely comminuted and especially in compound fractures type III, we have used the pins and plaster method but prefer to use an external fixateur, type Roger Anderson or Hoffman. This facilitates wound care and provides excellent stability, but should be removed as soon as early callus appears on roentgenograms and no later than six weeks, because of the increased incidence of delayed union, also noted by the authors. With the methods of treatment available today the indication for open reduction of a tibial shaft fracture is rarely, if ever, present. Even in the best hands infection is always a risk and delayed union and nonunion can also be a problem. A segmental fracture or one associated with a vascular injury requiring repair are relative indications for open reduction and internal fixation. In these instances, ASIF instrumentation is probably the best available method today. But its indiscriminate use can only lead to serious and unnecessary complications.

Miguel E. Cabanela, M.D.†
Rochester, Minnesota

*Kennedy T et al.: Management of tibial fractures. Minnesota Med 58:525, 1975.
†Orthopedic Surgery, Mayo Clinic.



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Viruses and Kidney Disease

In the investigation of causes of kidney disease there is often first an attempt to establish an animal model that is similar to a human nephropathy. Sometimes the animal model is spontaneous, while others are induced as part of the investigation.

Howard and Balfour* have summarized the current literature dealing with the proven spontaneous and experimentally induced viral infections and their association with kidney disease both in animals and man. When it comes to man, the information is less firm, and certain findings must be reconciled. These include, the frequency of positive viral cultures from kidney and urine without demonstrable renal lesions; also, when there are renal lesions in the presence of a viral infection, the inability to establish with certainty a cause and effect relationship. Furthermore, questions must be asked, for example, if there is a definite relationship between viral infections and kidney lesions, why are renal changes absent in most instances of viral infection, transient in some, and what conditions are present to produce permanent injury in others?

A firmer understanding between viral infections and renal injury has come about recently in the observations of viral antigen-antibody complex mediated chronic glomerulonephritis. Much work is further needed, however, in the areas of specific identification of viruses as antigens and immunologic mechanisms that may link organism and organ.

*See page 809.

†Division of Nephrology, Department of Medicine, Mayo Clinic and Mayo Foundation.

James V. Donadio, Jr., M.D.†
Rochester, Minnesota

Serum Alpha-Fetoprotein*

Fraley et al. have shown that in appplication of the marker principle to diagnosis of nonseminomatous testicular cancer two tests are better than one. Using very sensitive assays for two markers, the beta subunit of human chorionic gonadotropin and alpha-fetoprotein, they observed a higher percentage of positive results in nonseminomatous testicular tumor using two tests than when either was used alone.

The search for markers in diagnosis and follow-up of malignant disease dates to early studies of Hertz (1961) et al. in gestational trophoblastic disease. In subsequent years, ectopic production of substances resembling human chorionic gonadotropin was reported in isolated cases of bronchogenic carcinoma, hepatoma, adrenal cortical carcinoma, melanoma, breast cancer and renal cell carcinoma. With development of more sensitive radio-immunoassay techniques for beta subunit of chorionic gonadotropin, it was possible to detect this hormone in cancers of the testicle, gastrointestinal tract, breast, malignant melanoma, leukemia, multiple myeloma, sarcomas and others.

Alpha-fetoprotein has also been detected in tumors other than hepatoma, principally in testicular cancer, and in small quantities in some nonmalignant conditions. The use of two such marker assays has proved to be of value in the detection of nonseminomatous testicular cancer, and studies of these investigators using this two-pronged approach will result both in better early diagnosis and in improved prospects for early detection of recurrences.

*See page 813.

Robert A. Green, M.D.
St. Louis Park Medical Center

Minnesota Urological Society

Minnesota Urological Society will meet at L'hotel Sofitel on Friday, November 21, for the purpose of conducting Pyelogram Conferences. Contact: William E. Price, M.D., Secretary, Metropolitan Medical Building, Minneapolis 55404.



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Laboratory Medicine

Interpreting Partial Thromboplastin Times

J. ROGER EDSON, M.D.*

THE PARTIAL THROMBOPLASTIN time is sensitive to changes in the intrinsic plasma coagulation pathway (all the plasma coagulation factors with the exception of Factor VII). High levels of plasma coagulation factors shorten the PTT, while low levels of clotting factors or inhibitors will prolong the PTT. These effects are more or less algebraically additive. Thus it is not possible to interpret a partial thromboplastin time without knowing something about the patient from which the specimen came. A list of things that result in high plasma coagulation factor activity and shortening of the PTT are given in Table 1.

TABLE 1
High Clotting Factor Levels Shorten the PTT

Activation of sympathetic nervous system (increased Factor VIII)
Hyperthyroidism (increased Factor VIII)
Estrogens (increased fibrinogen, Factors II, VII, VIII, IX, X)
Glucocorticoids (marked increase in Factors II, V, VIII, XI, moderate increase in Factors VII, IX, X, normal fibrinogen, Factor XII, serum FSP)
Slow intravascular clotting (increased Factors VIII, V, [IX] fibrinogen)
Nephrotic syndrome (increased Factors VIII, V, fibrinogen)
Activation of Factor V and VIII in blood drawing.

Activation of the sympathetic nervous system may result in a two to threefold rise in Factor VIII activity within five to 10 minutes. Thus the patient who has a 30% Factor VIII activity in the basal state may have a Factor VIII activity near to 100% when fully stimulated. His basal PTT would be prolonged, while his stimulated PTT would be normal. A patient with 25% Factor IX activity in the basal state would have a prolonged PTT. With an activated sympathetic nervous system, his Factor VIII activity might be 250%, and the partial thromboplastin time normal. In order to interpret Factor VIII values, one has to know if the patient had an activated sympathetic nervous system. In addition to the usual signs of sympathetic nervous system activity, there is an elevation of the platelet count to about one and one-half times the base line value.

Low concentrations of thrombin increase the activities of Factor V and Factor VIII. If a small amount of thrombin is generated in blood drawing before the specimen is mixed with the citrate anticoagulant for a coagulation specimen, this will increase Factor V and VIII activity and shorten the partial thromboplastin time over what it otherwise would have been. The effects of steroid hormones on the plasma coagulation system appear to be dose related. Slow intravascular activation of clotting regularly results in reactive increase of several hemostatic components. In the nephrotic syndrome, principally because of high Factor VIII activity, the PTT is usually short.

Low levels of plasma coagulation factors will prolong the partial thromboplastin time as indicated in Table 2.

TABLE 2
Low Levels of Clotting Factors Prolong the PTT

Inherited deficiencies
Vitamin K factor deficiency (including patients on Coumadin)
Liver disease (generally)
Massive transfusion with bank blood or volume expanders
Severe hypothyroidism

Because the partial thromboplastin time is more sensitive to deficiency states than the prothrombin time, it generally becomes prolonged in liver disease before the prothrombin time.

Inhibitors that prolong the PTT are listed in Table 3.

TABLE 3
Inhibitors prolong the PTT

Lupus inhibitor
Heparin
Dysproteinemias
Antibodies to (inactivators of) clotting factors

*Director, Coagulation Laboratory, Department of Laboratory Medicine and Pathology, University of Minnesota.

Adapted from Grand Rounds presentation, March 14, 1975.

The lupus inhibitor occurs in patients with autoimmune disorders, including lupus erythematous. When plasma from a lupus inhibitor patient is mixed with that from a normal individual, the PTT on the mixture is as long as that of the patient itself, or longer. Heparin prolongs the PTT to a variable degree depending on the test system. In dysproteinemias, anti-Factor VIII macroglobulins, antithrombin light chains, and mass action inhibition of polymerization by large amounts of paraprotein have been observed. Autoantibodies to Factors V, VIII, and IX, have been reported; all will result in a prolonged PTT.

In Table 4 a number of examples of partial thromboplastin times using University of Minnesota Coagulation Laboratory values are given. Please note again how activation of the sympathetic nervous system can mask a mild to moderate Factor VIII deficiency. The last entry in the table is from an actual patient. This was a young man with a Guillain-Barré syndrome who was placed on 100 mg of prednisone daily, developed thrombophlebitis and pulmonary embolism, and was placed on heparin. Prior to being heparinized, his PTT was 22 seconds. With a heparin concentration of 0.8 units/ml on a constant infusion, he developed gastrointestinal bleeding, in part due to heparinemia. In spite of the heparin concentration, because his Factor VIII activity was so high, the partial thromboplastin time was actually short. It cannot be over emphasized that if one is to interpret a PTT, one must know something about the patient from which the specimen came.

TABLE 4

	Kaolin PTT, seconds
Normal, basal state	35-45
Pregnancy, 3rd trimester	30-35
Cushing's syndrome	<30
Factor VIII <40% (other factors normal)	>45
Cord plasma	50-85 (mean = 65)
Nephrotic syndrome	<35
Frightened normal	30
Frightened patient with mild Factor VIII deficiency in basal state	40
0.5 units of heparin/ml normal plasma	60
0.8 units/ml heparin, 1200% Factor VIII	32

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Virus Infections and Kidney Disease—Howard and Balfour (page ....)

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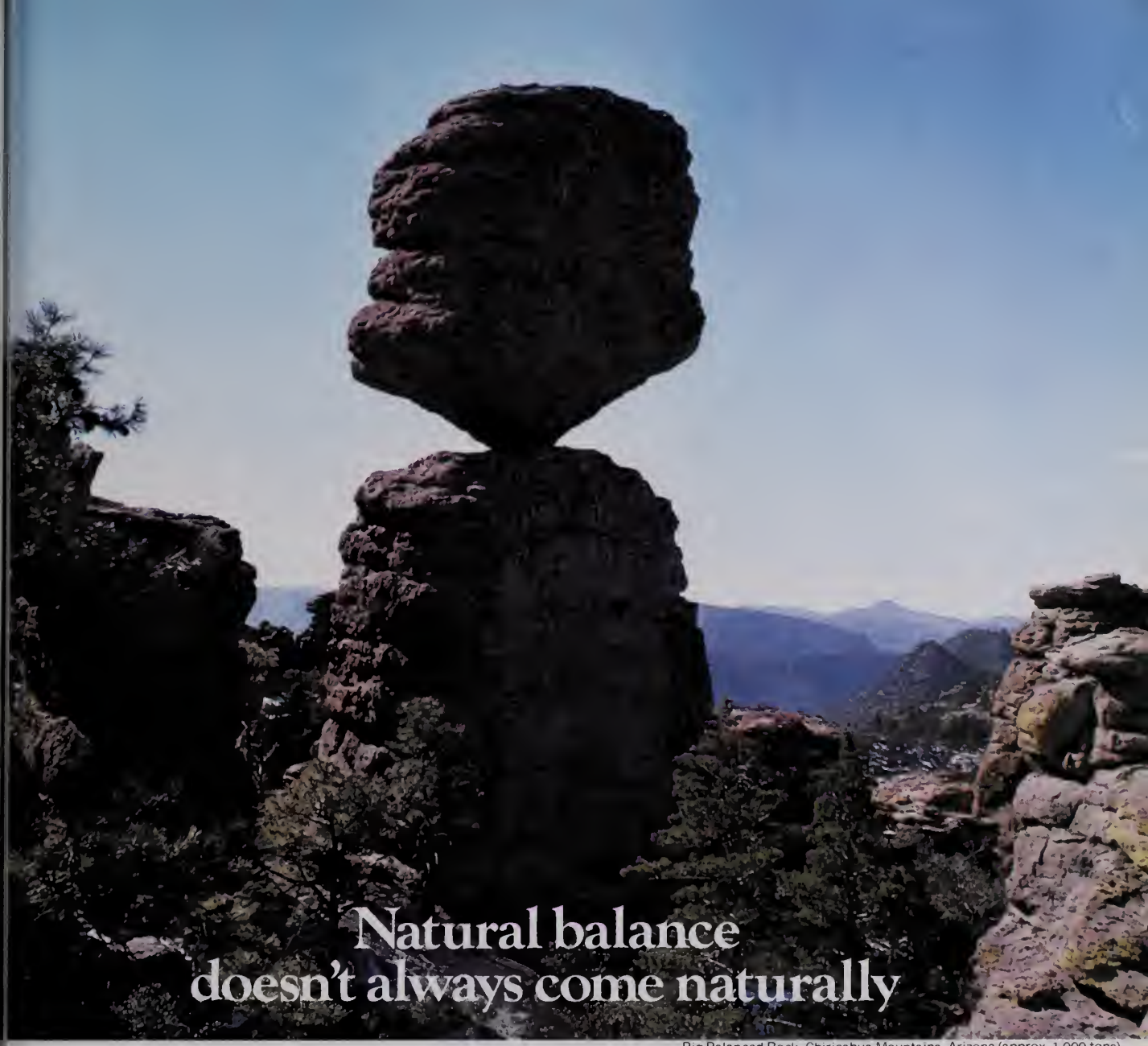
Cover Photo

"The Ruffed Grouse—Royalty of Upland Game"

Dr. Owings W. Kincaid in diagnostic roentgenology at the Mayo Clinic in Rochester told the editors "if I had but one month to live, I would hope to spend part of it at least in partridge country. The Ruffed Grouse is the royalty of upland game, and where he exists in great numbers true wilderness exists. A covert is, indeed, a treasure, and he who shares its exact location does so only with a true friend.

"The magnificent female 'Ruff' shown on the cover was taken in Michigan's upper peninsula during the month of October in 1972."

Dr. Kincaid used a Pentax Spotmatic with 50 mm lens, and the film was Kodak's high speed Ektachrome.



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IEF SUMMARY OF PRESCRIBING INFORMATION

*INDICATIONS. Based on a review of this drug by the National Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:

Effective: Management of nausea and vomiting and dizziness associated with motion sickness.

Possibly Effective: Management of vertigo associated with diseases affecting the vestibular system.

Final classification of the less than effective indications requires further investigation.

CONTRAINDICATIONS. Administration of Antivert (meclizine HCl) during pregnancy or to women who may become pregnant is contraindicated in view of the teratogenic effect of the drug in rats.

The administration of meclizine to pregnant rats during the 12-15 day of gestation has produced cleft palate in the offspring. Limited studies using doses of over 100 mg./kg./day in rabbits and 10 mg./kg./day in pigs and monkeys did not show cleft palate. Congeners of meclizine have caused cleft palate in species other than the rat.

Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

ADVERSE REACTIONS. Drowsiness, dry mouth and, on rare occasions, blurred vision have been reported.

More detailed professional information available on request.

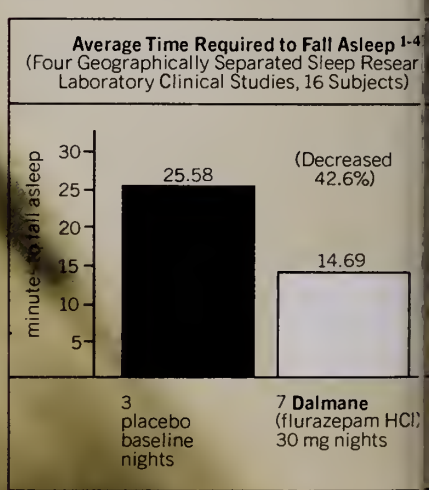
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A division of Pfizer Pharmaceuticals
New York, New York 10017

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(meclizine HCl) 25 mg. Tablets
for vertigo*

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..sleep research laboratory ıical studies prove: Dalmane ːreases number of nighttime akenings and increases total ep time.[5]

Dalmane (flurazepam HCl) relatively safe, seldom uses morning "hang-over"

Dalmane is generally well erated. The usual adult dose of mg should initially be lowered to mg for the elderly and ɔilitated, to help preclude ersedation, dizziness or ataxia. praisal of possible risks is ggested before prescribing.

FERENCES:

Caracan I, Williams RL, Smith JR: sleep laboratory in the investigation leep and sleep disturbances. Scientific ibit at the 124th annual meeting of the erican Psychiatric Association, shington DC, May 3-7, 1971

Frost JD Jr: A system for automati- y analyzing sleep. Scientific exhibit at 24th annual Clinical Convention of the erican Medical Association, Boston, 29-Dec 2, 1970; and at the 42nd ıual scientific meeting of the Aerospace dical Association, Houston, Apr 26-29, 1

Vogel GW: Data on file, Medical Depart- ıt, Hoffmann-La Roche Inc., Nutley NJ

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ore prescribing Dalmane (flurazepam l), please consult complete product ɔrmation, a summary of which follows:

ications: Effective in all types of insomnia racterized by difficulty in falling asleep, quent nocturnal awakenings and/or early rning awakening; in patients with recurring ɔmnia or poor sleeping habits; and in te or chronic medical situations requiring tful sleep. Since insomnia is often transient l intermittent, prolonged administration is erally not necessary or recommended.

Contraindications: Known hypersensitivity to flurazepam HCl.

Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. Caution against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Use in women who are or may become pregnant only when potential benefits have been weighed against possible hazards. Not recommended for use in persons under 15 years of age. Though physical and psychological dependence have not been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage.

Precautions: In elderly and debilitated, initial dosage should be limited to 15 mg to preclude oversedation, dizziness and/or ataxia. If combined with other drugs having hypnotic or CNS-depressant effects, consider potential additive effects. Employ usual precautions in patients who are severely depressed, or with latent depression or suicidal tendencies. Periodic blood counts and liver and kidney function tests are advised during repeated therapy. Observe usual precautions in presence of impaired renal or hepatic function.

Adverse Reactions: Dizziness, drowsiness, lightheadedness, staggering, ataxia and falling have occurred, particularly in elderly or debilitated patients. Severe sedation, lethargy, disorientation and coma, probably indicative of drug intolerance or overdosage, have been reported. Also reported were headache, heartburn, upset stomach, nausea, vomiting, diarrhea, constipation, GI pain, nervousness, talkativeness, apprehension, irritability, weakness, palpitations, chest pains, body and joint pains and GU complaints. There have also been rare occurrences of leukopenia, granulocytopenia, sweating, flushes, difficulty in focusing, blurred vision, burning eyes, faintness, hypotension, shortness of breath, pruritus, skin rash, dry mouth, bitter taste, excessive salivation, anorexia, euphoria, depression, slurred speech, confusion, restlessness, hallucinations, and elevated SGOT, SGPT, total and direct bilirubins and alkaline phosphatase. Paradoxical reactions, *e.g.*, excitement, stimulation and hyperactivity, have also been reported in rare instances.

Dosage: Individualize for maximum beneficial effect. *Adults:* 30 mg usual dosage; 15 mg may suffice in some patients. *Elderly or debilitated patients:* 15 mg initially until response is determined.

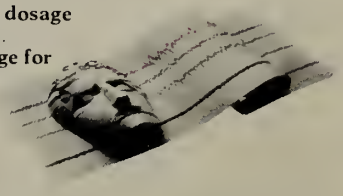
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Opinion & Dialogue

Should a specially prepared package insert be made available to patients?



Dr. Alexander M. Schmidt
Commissioner,
Food and Drug
Administration



Dr. James H. Sammons
Executive Vice President
of the American
Medical Association

The idea of a so-called patie
package insert has been around
a long time. Many physicians alre
use written instruction sheets to
provide patients with informatior
about the drugs they are taking.
some physicians give verbal instr
tions; but in too many instances
these are what I call eye-glazing e
ercises. I have seen patients sit w
glazed eyes listening to a rapid-fi
lecture by a hurried physician wh
has 20 people out in his waiting
room. These patients aren't giver
sufficient understanding and the
fore do not follow instructions. S
think the idea of an official packa
insert for patients is a good one.
Perhaps we should really think of
this kind of information simply as
extension of drug labeling.

The benefits of patient involveme

Many physicians may not re
ize how frequently a patient obta
his drug information from Aunt
Tillie or the next door neighbor. A
this information is almost alway
bad or irrelevant to the case at ha
Furthermore, the incentive to go
along with a prescribed program
slim if the only reading matter th
patient receives, along with his p
scription, is a bill.

As an educator I am impres
by the principle that the best way
get someone to do something is t
involve him in the process. So the

I think there are advantages
well as some real disadvantages
a patient package insert. When y
begin to use semi-medical or me
cal terms to describe complicatio
or possible sequelae of disease o
treatment, you may frighten the p
tient—particularly since the more
highly sophisticated patient is no
the one who is going to read the i
sert. The patient who will read it i
the one most susceptible to frigh
and confusion by the language.

On the positive side, a pack
insert will probably give the patie
better insight into why he is being
treated the way he is, and it may
give the physician a little bit more
time. But it does not remove from
the physician the need or obligat
to explain the insert.

Some pitfalls in the inclusion of side effects

Certainly a patient should b
warned of the possibility of seriou
side reactions—to know what the
real dangers are. But it doesn't do
bit of good to indicate that a patie
on oral penicillin may develop a
rash, itching, or a drop in blood
pressure. Or that he may faint. I
think the real danger is that frigh
engendered by the insert may po
sibly outweigh the potential good

ain purpose of drug information r the patient is to get his coopera- on in following a drug regimen.

reparation and distribution of atient drug information

We would hope to amass infor- ation from physicians, medical cieties, the pharmaceutical indus- y and centers of medical learning. he ultimate responsibility for uni- rm labeling must, however, rest ith the Food and Drug Administra- on. There is nothing wrong with is agency saying, "this informa- on is generally agreed upon and erefore it should be used," as long s our process for getting the infor- ation is sound.

Distribution of the information a problem. In great measure it ould depend on the medication in uestion. For example, in the case f an injectable long-acting proges- rone, we would think it mandatory issue two separate leaflets—a ort one for the patient to read be- re getting the first shot and a long ne to take home in order to make a ecision about continuing therapy. this case, the information might e put directly on the package and ot removable at all. But for a medi- ation like an antihistamine this formation might be issued sepa- ately, thus giving the physician the ption of distribution. This could reserve the placebo use, etc.

It is in the distribution of patient information that the pharmacist may get involved. As professionals and members of the health-care team and as a most important source of drug information to patients, pharmacists should be responsible for keeping medical and drug records on patients. It is also logical that they should distribute drug information to them.

Realistic problems must be considered

We have to expect that the introduction of an information device will also create new problems. First, how can we communicate complex and sophisticated information to people of widely divergent socioeconomic and ethnic groups? Second, what will we say? And third, how can we counteract the negative attitude of many physicians toward any outside influence or input? Hopefully the medical profession will respond by anticipating the problems and helping to solve them. Assuming we can also solve the difficulty of communicating information to diverse groups throughout the United States, our remaining task will be the inclusion of appropriate material.

What information is appropriate?

In my opinion, technical, chemical and such types of material should not be included. And there is no point in the routine listing of side effects like nausea and vomiting which seem to apply to practically all drugs, unless it is common with the drug. However, serious side effects should be listed, as should information about a medication that is potentially risky for other reasons.

Other pertinent information might consist of drug interactions, the need for laboratory follow-up, and special storage requirements. What we want to include is information that will help increase patient compliance with the therapy.

Positive aspects of patient drug information

Labeling medication for the patient would accomplish a number of good things: the patient could be on the lookout for possible serious side effects; his compliance would increase through greater understanding; the physician would be a better source of information since he would be freer to use his time more effectively; other members of the health-care team would benefit through patient understanding and cooperation; and, finally, the physician-patient relationship would probably be enhanced by the greater understanding on the part of the patient of what the physician is doing for him.

---

nly the doctor can remove that fear y 20 or 30 minutes of conversation.

I'm not suggesting that we ithhold any information from the atient because, first of all, it would e totally dishonest and secondly, it ould defeat the very purpose of the nsert. I do think that a patient on the irth control pill should know about ne incidence of phlebothrombosis.

If you're going to tell a patient ne incidence of serious adverse re- ctions, then you have to tell him nat a concerned medical decision as made to use a particular medi- ation in his situation after careful onsideration of the incidence of omplications or side effects.

motionally unstable patients pose special problem

There are patients who, be- ause of severe emotional problems, ould not handle the information ontained in a patient package in- ert. Yet if we are going to have a ackage insert at all, we just can't ave two inserts. I think we might imply have to tell the families of hese patients to remove the insert rom the package.

egal implications of the patient ackage insert

Just what effect would a patient package insert have on malpractice? We could try to avoid any legal implications by pointing out that the physician has selected a particular medication because, in his professional judgment, it is the treatment of choice. For instance, you can't tell everyone taking antihistamines not to work just because a few patients develop extreme drowsiness which can lead to accidents. And what about the very small incidence of aplastic anemia rarely associated with chloramphenicol? If, based on sensitivity studies and other criteria, we decide to employ this particular antibiotic, we do so in full knowledge of this serious potential side effect. It's not a simple problem.

How do we handle an insert for medication used for a placebo effect?

With rare exceptions, physicians no longer use medications for a placebo effect. This question does raise the issue of how a patient may react to receiving a medication without a package insert.

Preparation of the package insert

The development of the insert ought to be a joint operation between physicians, the pharmaceutical industry, the A.M.A. and the F.D.A.

I view the A.M.A.'s role as a coordinator or catalyst. It is the only organization through which the profession as a whole, irrespective of specialty, can speak. It has relatively instant access to all the medical expertise in this country. And it can bring that professional expertise together to ensure a better package insert. The A.M.A. can work in conjunction with the industry that has produced the product and which is ultimately going to supply the insert.

I don't think we should rely, or expect to rely, on legislative committees and their nonprofessional staffs to make these decisions when it is perfectly within the power of the two groups to resolve the issues in the very best American tradition—without the government forcing us to do it. I think the F.D.A. has to be involved, but I'd like them to become involved because they were asked to become involved.

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Legislative

MSMA Statement on Professional Liability

as presented by
G. R. Diessner, M.D. President

to the Special Senate Subcommittee on Medical Malpractice, Aug. 22, 1975 and the House Joint Subcommittee on Medical Practice, September 9, 1975.

Mr. Chairman and members of the Subcommittee. I am Dr. G. R. Diessner, President of the Minnesota State Medical Association. We appreciate this opportunity to address the problems of medical liability insurance as they relate to the practice of medicine in Minnesota and as they affect the cost of delivering medical care. With me today are Dr. Edward L. Seljeskog, President of the Minnesota Neurosurgical Society, Dr. Van Lawrence representing the Minnesota Society of Anesthesiologists and Dr. Chester Anderson, Chairman of the Minnesota State Medical Association Committee on Public Policy.

Drs. Seljeskog and Lawrence will outline for you some of the specific problems in professional liability as they affect the so-called "high risk" physicians, doctors who by virtue of the specialized procedures they perform, become more vulnerable to suit. Dr. Anderson will then conclude our presentation with legislative proposals which if enacted we believe would provide some immediate relief to the rapidly escalating costs of professional liability insurance.

At the outset I would like to state that despite marked increase in malpractice insurance premium costs, as of January, 1975, Minnesota rates were the 36th *lowest* among the states in the cost for basic coverage. Despite this relatively low ranking, premiums have almost tripled for many Minnesota physicians in the last five years and some specialists are paying over $10,000 a year for such protection.

Minnesota physicians may, however, be considered more fortunate than those in many other states as they *do* have coverage available to them. There is increasing concern that the amount of "excess coverage" that the St. Paul Companies are willing to provide will not adequately insure the high risk specialists. By "excess coverage" we mean the amount of insurance coverage over and above the $100,000/300,000 basic insurance coverage on which current rates are based. This will be discussed in more detail later.

The semi-retired or part-time physician also faces a particular dilemma. Current underwriting practices dictate that regardless of how few patients a physician treats or how many days or weeks each year he or she practices, the insurance premium is the same. As premium costs have escalated an increasing number of doctors with small or part time practices, who fill a valuable community need, are considering complete retirement because their income can no longer support the cost of malpractice insurance.

We are fortunate in Minnesota that we have not experienced situations such as occurred in California and New York where groups of physicians, threatened with loss of insurance coverage or considerable increases in premiums, were felt compelled to withhold their services in order to secure favorable legislation or other redress. To state that our malpractice insurance costs are lower than the national averages and that an insurance market does exist in Minnesota speaks well for the quality of medical care delivered. All this, however, is not to say that we have a pleasant situation in Minnesota—quite the contrary. We, too, are facing a crisis in professional liability that is growing rapidly. In 1970, according to the St. Paul Companies, there were 121 claims filed against Minnesota physicians for a ratio of one of every 29 doctors insured; in 1974, this figure had risen to 305 claims filed for a ratio of one claim for each 13 physicians. During the first six months of 1975, 158 claims have already been filed. A tabulation of pending claims showed the 4300+ Minnesota physicians insured by St. Paul Companies have a total of 472 outstanding claims against them. The majority of claims are ultimately dismissed as without merit but it is nevertheless extremely expensive to defend them. Yet awards or settlements that are ultimately made have increased substantially in size as well as in number. Why? . . .

A number of causes can be cited as contribut-

ing to the dramatic increase in claims. Americans generally are caught up in a legal rights explosion. Citizens are quicker to sue when they feel their rights have been violated. Consumerism has educated patients to understand that a lawsuit is simply another means of gaining redress of their grievances, real or imaginary. A greater number of plaintiff attorneys have also become interested in medical malpractice litigation. In addition, the "contingency fee" system whereby plaintiff attorneys charge their clients from ⅓ to ½ of any claims payment or award has in the opinion of many physicians contributed greatly to the escalation of malpractice insurance costs.

Higher patient expectations have also contributed to the current professional liability cost. Despite tremendous medical advances, doctors still cannot guarantee success from every surgery, every treatment, every prescription. Television and other communications media, however, have led many people to have unrealistic expectations. Only television doctors can spend unlimited time with patients, make countless house calls and seldom give less than perfect care.

The doctor-patient relationship is less personal today for many reasons including the increased specialization and workload of the physicians, the use of screening examinations and disease programs, and the mobility of Americans. Even though medical care is more efficient and more effective, unfortunately, there is often less opportunity for personal communications between patient and physician. The practice of medicine is complex and growing more so. New techniques and new drugs increase diagnostic acumen, ease suffering, and save lives that would have been lost before but they also bring new and at times increased risks. Patients must understand this fact.

The insurance risk of medical liability is actually quite unique. The best result that can be achieved for those injured, disabled or ill is often only an improvement in the condition and not a return to the normal state. Even with the best and most effective care, the patient may be dissatisfied with the results of medical services and is, at least theoretically, a potential claimant. In no other human relationship does an equivalent potential for litigation exist. As a practical matter, most patients do not make liability claims if the results are satisfactory or within the limits of their expectations. But "satisfaction" and "expectation" are vague and subjective concepts and subject to change. What were satisfactory results ten years ago may not be considered satisfactory today. It is frequently forgotten that the outcome is only partly in the control of the physician or hospital as the patient and his behavior are also significant factors in achieving an optimum result.

Since physicians are human beings, they are subject to human error and to variations in quality of performance. Some unsatisfactory results for patients are undoubtedly caused by such error or variation in performance. Contrary to assertions made by some, however, the incompetent physician is not the culprit insofar as the cause of most malpractice litigation. Insurance records indicate that the relative competency of the doctor is not a major factor in the incidence of professional liability claims, that even the most skillful surgeon or qualified physician faces suits with increasing frequency. Where medical incompetence does exist the profession is demonstrating an increasing willingness to deal with the problem through strict peer review. Only last session this legislature enacted new legislation sponsored by the MSMA providing for immunity from suit to hospital committees who determine a physician's fitness for medical staff privileges. This legislation will permit more objectivity and encouragement in determining whether or not a physician should be granted staff privileges.

To reduce the frequency of allegations of negligence, physicians are turning increasingly to the practice of what is called "defensive medicine." The threat of possible malpractice litigation is undoubtedly motivating more and more physicians to perform extra tests and procedures on the one hand and to decline to undertake risky but indicated procedures on the other. The assertion that the former type of defensive medicine has led to an increase in the cost of medical care is quite likely true.

A survey published in 1974 by Medical Economics indicated that a majority of physicians have altered their practice patterns to some extent because of concern over legal liability. When asked how the safeguards, such as increased lab tests, more consultations, more referrals, more hospitalizations and more follow-up notes, affected the quality and cost of medical care, the consensus of physicians interviewed was that concern over malpractice litigation had raised the overall standards of care but had increased the costs of delivering medical care.

What else are physicians doing about the costs

of professional liability? Inasmuch as the cost of defending this increased volume of claims in court has become staggering, we are looking to arbitration as a cost effective and fair means of settling malpractice disputes. It is estimated that 50 cents of each malpractice insurance dollar is set aside for litigation defense costs and leaves no more than 15-25 cents of each dollar for the successful claimant after his legal fees and expenses of litigation are paid. At present when a case is considered non-meritorious or agreement cannot be reached on the amount of loss, the case goes to trial where legal costs mount rapidly.

Binding arbitration offers in our view the most promise for speeding up the disposition of claims, reducing settlement and defense costs, and of overcoming jury decisions based on emotions instead of law and facts. The Minnesota State Medical Association and the Minnesota State Bar Association have just recently endorsed and are now beginning to implement a pilot plan for voluntary binding arbitration in the seven county metropolitan area. The plan basically calls for the formation of arbitration panels composed of a lawyer selected from a panel chosen by the Bar Association, a physician selected from a panel chosen by the Medical Association, and a lay person. Agreement between the plaintiff and the defendant to arbitrate an existing claim is voluntary. The arbitration panel in effect is a sophisticated three person jury well equipped to comprehend the legal and medical aspects of the claim. The panel will render a decision on both issues of negligence and damages which, because the decision is binding, will not be subject to the usual long costly appeal process. The MSMA is opposed to plans for arbitration that are not binding on the participants. Other types of arbitration or screening panel approaches whose decisions are not binding have been suggested. However, under these plans if the plaintiff loses, or if the award of damages is not as large as he thinks it should have been, he may still go to court.

Finally, and probably most important, we must emphasize that changes by the courts in negligence law are steadily eroding many of the traditional legal defenses customarily available to doctors. Dr. Anderson will detail these to you in later testimony: however, I must emphasize that certain remedial legislation is necessary to prevent the complete collapse of legal defenses. The legislature and the public must recognize that doctors cannot be expected to be infallible and there must be some protection under the law. Legislation to accomplish this, however, must be clearly in the public interest. We are not interested in legislating changes in the tort system that benefit only physicians and work to the detriment of patients who may have suffered adverse results from negligent medical care. Paramount to our consideration, as is yours, is the protection of the interests of all parties involved in a medical malpractice litigation.

As you address yourselves to the various legislative remedies that have or will be brought forth we urge you to move carefully and cautiously. Over 20 states have already enacted a wide variety of proposals but in great part they are untested or unproven. There are no instant solutions or panaceas to the problem and hastily enacted legislation based on unproven premises or theories could actually worsen the professional liability insurance situation in Minnesota. We need only to look to our sister state of Wisconsin to see an example of a malpractice legislative package passed and signed into law just last month that no one is happy with. According to the Wisconsin State Insurance Commissioner, the legislature passed a bad bill which will create an administrative nightmare. It should behoove us to watch carefully during the next year or two the experience of Indiana, Ohio, Idaho, Tennessee, Florida and other states that have enacted comprehensive laws. This is not to mean we wish inaction on the part of the legislature. There are a number of defects in our tort system which should be remedied now to keep the lid on a serious problem. The enactment of these proposals will not only slow the rate of premium escalation but will help insurors to continue to make coverage available for the physicians of Minnesota.

The Minnesota State Medical Association is therefore asking your help in seeking reasonable solutions to the problem and we pledge our cooperation and assistance to you in any way we can,

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The December issue of MINNESOTA MEDICINE will carry a presentation on medical malpractice by Chester A. Anderson, M.D., Chairman of the Committee on Public Policy discussing specific legislative proposals designed to remedy the growing crisis in professional liability insurance.

MSMA Annual Meeting

The Way We Were . . .

One hundred years ago, Minnesota physicians confronted scores of diseases that meant certain death. Today, all but the names of those diseases are extinct. Archaic procedures and medications prevalent during our state's infancy have been abandoned and continually replaced by improved methods of treatment making the present level of health care in Minnesota a bench mark for others. There is no doubt that continuing medical education has played an extremely vital role in maintaining this excellence.

The MSMA Annual Meeting provides outstanding CME opportunities through its scientific sessions. This year, credits in cardiopulmonary resuscitation, chemical dependencies, crisis intervention and eight other varied and timely subjects will be offered in Rochester. Program sponsors for 1976 include the Minnesota Heart Association; Minnesota Chapter, American College of Surgeons; Minnesota Obstetrical and Gynecological Society; Minnesota Chapter, American Academy of Pediatrics; several MSMA committees and a group of Methodist Hospital staff.

The scientific program of the Annual Meeting is an enjoyable, convenient way to stay abreast of the latest in medicine, a fine example of continuing medical education and a great way to earn necessary CME credits for MSMA membership. Most important, however, the scientific program and all accredited CME activities keep Minnesota physicians the way we are, moving ever forward professionally from the way we were. . .

R. D. Semsch, M.D.
Chairman
Scientific Assembly

Minnesota Medical Information Service Discontinues Operation

On November 30, 1975 the Minnesota Medical Information Service will be discontinued. The program, which was begun in 1972 as an expansion of the Dial Access Program for physicians, was funded initially by Northlands Regional Medical Program and later by the University of Minnesota. The four services provided by MMIS included: (1) Dial Access Tapes (2) Library Service (3) Drug Information Service (4) Medical/Dental Advisory Service.

It has been well documented by this and other programs that utilization of the service declines without continued promotion. Therefore, it is questionable if the system is needed by health practitioners, because they have other alternative methods of obtaining the necessary information. When the program is evaluated on a cost effective basis, there are other methods which seem to have greater educational and informational payoff for similar input of resources. On the basis of these and other reasons, the decision has been made to discontinue the Minnesota Medical Information Service program, including the WATS long distance toll free line.

Physicians who wish to continue to utilize the free photocopy service provided by the Bio-Medical Library should give their requests to the librarian in their local hospital. For the computed assisted biblographical searches (Medline, Toxline) physicians may contact their local librarian or call the Medline office direct at (612) 376-7233 or 373-5584. Physicians wishing to contact specific physicians or departments at University Hospitals may wish to consult the University of Minnesota Hospital's *Directory of Service* book. If the directory is not available, call the University Hospital information operator at (612) 373-8484 for assistance.

Fracture Conference

Pathologic Fracture of the Distal Femur

FRANKLIN H. SIM, M.D.*; NORMAN H. ELLINGSEN, M.D.† and KENNETH A. JOHNSON, M.D.*

Dr. Franklin H. Sim:

This conference concerns the diagnostic and therapeutic challenge presented by a destructive lesion of the distal femur in which there is an associated fracture.

Case 1

Dr. Norman H. Ellingsen:

The patient is a 16-year-old girl whose initial complaints were a vague aching in her left knee and mild swelling after some physical activity in school. Two months after the onset of this problem, she was involved in an automobile accident. Xrays were taken immediately after the accident (Figure 1A).

Dr. Fink, would you describe the abnormalities on these Xrays?

Dr. Richard A. Fink:

The Xrays reveal a T-type intercondylar fracture of the distal femur. This fracture appears to have occurred through an osteolytic lesion in the femur.

Dr. Ellingsen:

Would you classify this as a pathologic fracture?

Dr. Fink:

Yes, because it occurred through an area of localized abnormal weakened bone.

Dr. Ellingsen:

Dr. Beabout, what would you consider in a differential diagnosis?

Dr. John W. Beabout:

Radiographically, the lesion appears to be benign, without evidence of invasiveness. The possibility of a cartilaginous tumor such as an enchondroma or chondromyxoid fibroma should be considered, as well as a giant-cell tumor and aneurysmal bone cyst.

Dr. Ellingsen:

The patient was initially treated in her home community with skeletal traction and a tibial pin, and within four weeks, she had "good callus formation." A closed biopsy had been done and the

*Consultant, Department of Orthopedics, Mayo Clinic and Mayo Foundation, Rochester, Minnesota.
†Resident in Orthopedics, Mayo Graduate School of Medicine (University of Minnesota), Rochester, Minnesota.
Reprint address: Dr. F. H. Sim, Mayo Clinic, 200 First Street SW, Rochester, MN 55901.

Fracture Conference, October 2, 1972

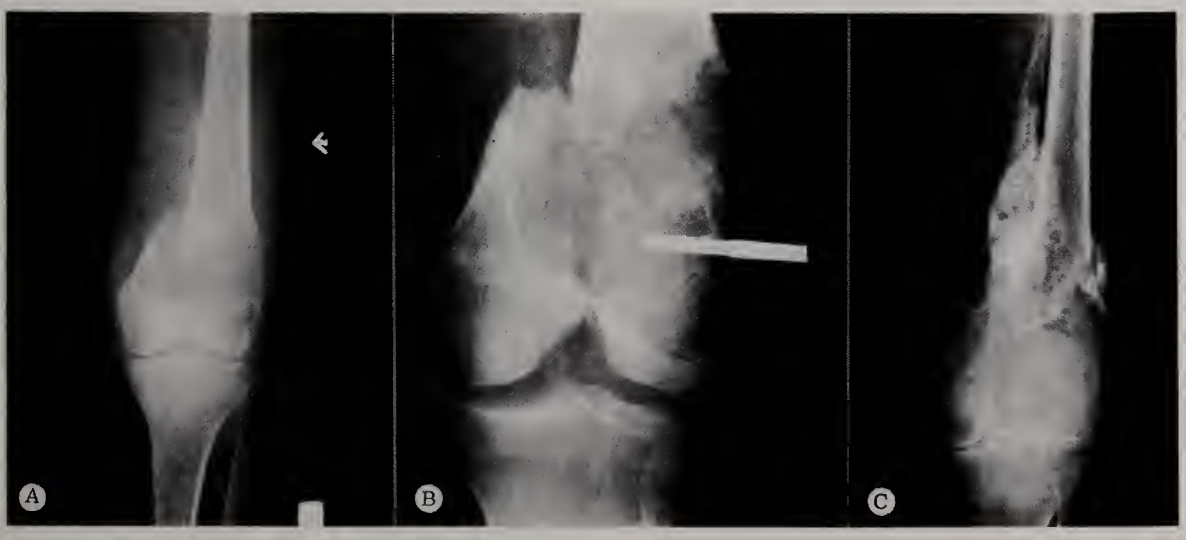


Fig. 1—*(A)* T-condylar fracture of distal femur superimposed on osteolytic bone defect. *(B)* Femoral lesion two weeks later at time of trochar biopsy. *(C)* Femoral lesion six months after fracture shows more extensive involvement of bone.

microscopic diagnosis was reported as being "consistent with fibrous dysplasia" (Figure 1B). The patient was next treated with a cast brace, but because of persistent pain, she came to our clinic six months after the initial fracture. These roentgenograms were taken at her initial examination at our clinic (Figure 1C) Dr. Beabout, would this roentgenogram alter your initial impressions?

Dr. Beabout:

The Xrays reveal much more bony involvement than was initially present. Just how much reflects actual bone healing is difficult to say, but a more invasive pattern is present at this time—suggesting malignancy.

Dr. Ellingsen:

The patient underwent open surgical biopsy. Pathologic study revealed a benign giant-cell tumor. Dr. Swanson, do you think the limb can be salvaged, or would you recommend amputation?

Dr. Gene E. Swanson:

Because of the possibility of malignancy, a wide en-bloc excision probably should be performed. However, this would leave a considerable bony defect. Perhaps one could consider either total knee arthroplasty, with the insertion of a custom-made prosthesis, or bone grafting.

Dr. James H. Dobyns:

I think we could also consider wide excision and homogeneous bone and joint replacement.

Dr. Sim:

Because the patient had no ligamentous stability after resection and because of her age, we elected not to insert a custom-made prosthesis. We believed that we could salvage the extremity, and after a wide en-bloc excision, including the distal five inches of the femur, we packed methyl methacrylate in the space to maintain the length. At a second operation, after obtaining a long custom-made Hansen-Street nail, we resected two and a half inches of proximal femur from the subtrochanteric area on the opposite leg, using a Harris blade-plate for fixation (Figure 2). We placed the two and a half-inch piece of bone into the area that was resected (Figure 3) and inserted an intramedullary nail through the proximal femur into the distal tibia through the graft.

Dr. Ellingsen:

Dr. Swanson, do you envision any difficulty with fixation if the procedure were terminated at this point?

Dr. Swanson:

There might be difficulty with rotational stability.

Dr. Ellingsen:

This was considered, and because we thought that this could happen, we added a plate. The patient was placed in a spica cast for five months. Seven months after surgery, the patient had no pain and no evidence of recurrence and used only one cane for support.

Comment

Dr. Sim:

This case involved a relatively long time from



Fig. 2—Harris blade-plate fixation after segmental shortening of one femur and intramedullary rod fixation of contralateral femur, which is lengthened distally by segment interposition.

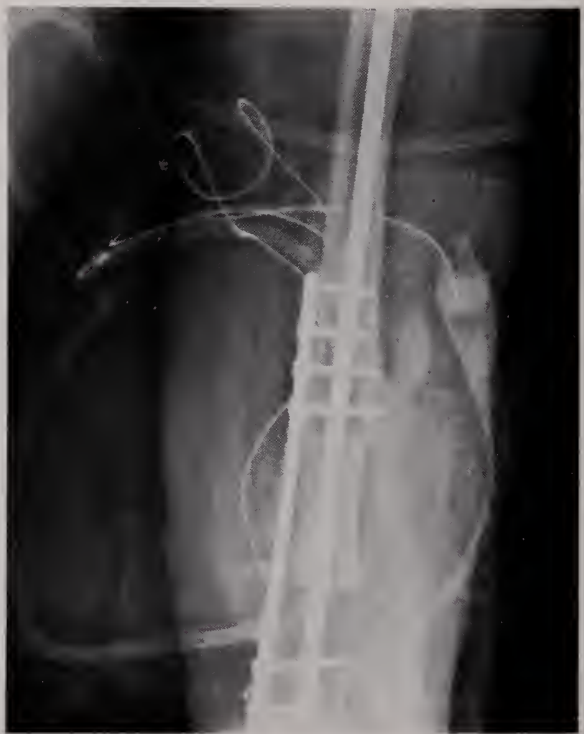


Fig. 3—Cylinder of transplanted femur fixed between femur and tibia.

onset of symptoms and x-ray findings to the final definitive treatment. No doubt one of the main reasons that difficulty is encountered in the management of bone tumors is their rarity. Unfortunately, the insidious nature of the lesions does not facilitate early diagnosis, and the first problem is to recognize that an osseous lesion exists. The problem is even more challenging when a patient presents with a pathologic fracture.

The interpretation of the Xrays in their proper perspective is important in the overall management of these lesions. The normal roentgenographic characteristics of the lesion are often distorted by the fracture, causing difficulty in interpretation of the roentgenograms. In many cases, too much emphasis is placed on the x-ray interpretation in deciding the appropriate management, resulting in a period of neglect, later to be followed by overt evidence of aggressiveness or malignancy.

The establishment of a definite diagnosis requires biopsy and microscopic study. Because appropriate management of these challenging problems is dependent on an accurate histologic diagnosis, this necessitates an adequate open biopsy. Too often the surgeon expects the pathologist to arrive at an accurate diagnosis based on an inconclusive needle biopsy.

Treatment includes complete eradication of the lesion, followed by skeletal reconstruction and restoration of function. The present case is characterized by an aggressive clinical course and extensive destruction. The problem is magnified when a pathologic lesion involves or destroys the joint. However, with the recent advances in reconstructive orthopedic surgery, satisfactory function of the proximal femur and hip joint after radical en-bloc resection may be obtained by use of a custom-made prosthesis to replace the resected bone. A total hip procedure is advised to prevent the complication of migrating femoral head, as has been previously reported by Wilson and Lance[1] when the femoral head and neck component only was used. In the area involving the distal femur, this method has been effective in restoring the skeletal integrity after extensive resection of the joint. A successful effort to save the extremity and to eradicate the tumor has resulted thus far. Dr. Ellingsen, will you comment on the literature?

Dr. Ellingsen:

Most of the literature on resection tumor surgery concerns giant-cell tumors, which often offer a challenge because of their proximity to the joint. Many authors believe that even though the tumor tends to recur, the difficulty of reconstructive surgery justifies at least one attempt at curettage and packing. However, Dr. Parrish,[2] in a 1966 report, stated his belief that curettage cannot remove all the neoplastic cells that lie within the bony interstices and irregular wall of the tumor. Therefore, he advocated that wide en-bloc excision to include all of the wall or pseudocapsule should be performed initially, especially in cases such as the present one in which marked thinning of the cortex was present and there was a possibility of malignancy. In four cases similar to the one presented, Parrish[2] resected the distal portion of the femur and replaced it with a homogeneous bone in the form of a hemijoint transplant. At the five-year follow-up, the patient had good range of motion with little instability and no pain. Complications that have arisen in other series are related to bone resorption, avascular necrosis, degenerative joint disease, and ligamentous instability.

In 1965, Wilson and Lance[1] described a patient with a giant-cell tumor who underwent en-bloc resection of the distal femur, followed by arthrodesis in which a large sliding tibial graft cut in a coronal plane was used to bridge the defect; internal fixation was obtained by use of a custom-made Küntscher nail. Two-year follow-up revealed a painless but shortened extremity with no limitation of activity.

Amputation as a primary treatment has been used in 10 cases of benign giant-cell tumor at the Mayo Clinic because of extensive local destruction and sometimes because of an erroneous diagnosis of sarcoma.

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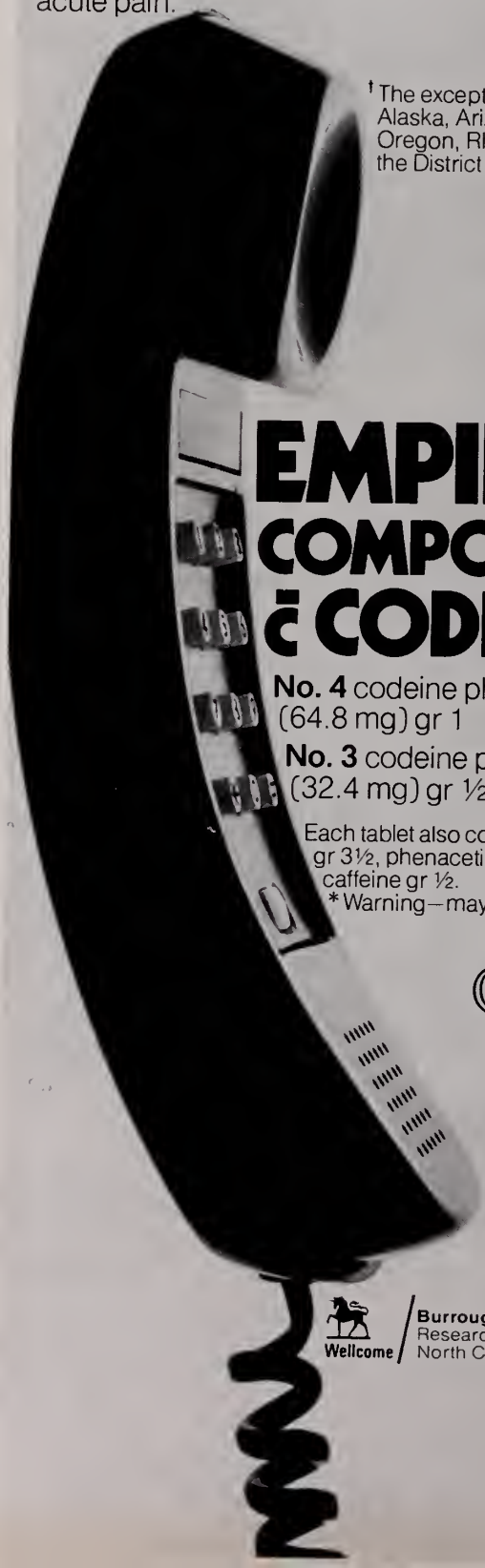
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2. Parrish FF: Treatment of bone tumors by total excision and replacement with massive autologous and homologous grafts. J Bone Joint Surg [Am] 48:968, 1966.

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Special Article

Medical Care in Hennepin County

Everyone Should Have A Cottage

JOHN E. SMITH, M.D.*

Our health care system is described as a cottage industry; a non-system. In this article the cottage system is explained, praised and offered as a standard of excellence which other systems must attempt to surpass.

THE PRACTICE OF MEDICINE is still a personal thing, a relationship between two people. At this personal level, medical care is neither a right nor a privilege. Grocers or plumbers have no more right to a physician's knowledge and time than he has to theirs. Like many things, medical care is an implied contract between a buyer and a seller. A doctor has something to offer: knowledge, skill and time. The patient has need of this knowledge, either to get well or to stay well. As best they can—within the imperfect state of the art—physicians teach patients how to do this. Doctors get paid for this exchange of knowledge and if it was worth it then they will be called on again. If the knowledge was too dear or not helpful, then a different source will be used next time. Doctors should also try to teach the reasons behind the advice, but beyond that there should be no coercion; none on either side. If they do enter into a contract for care then both have rights and obligations under the contract.

The Contract

The payment of a fee is a part of the patient's side of the contract. Even if the doctor is employed by a third party, there should be a payment of some kind pass between the patient and the physician. The amount is unimportant, the symbolism is all important. It means that the doctor is in his employ and under an obligation to serve his best interests.

I learned early in practice the importance of establishing this contract. First at the hospital where I was employed to care for the student nurses; it was reinforced when I became the company doctor for several industrial plants; but it was obvious also when I gave volunteer care to the local football team and at the Teen Center where I also was a volunteer. In all of these places, my care was less effective because I wasn't really that person's doctor. They hadn't hired me, so they never were quite sure whether my advice was best for the organization or best for them.

If I am working for a patient, then the patient has a certain control over the outcome. If I am working for a company, then the patient has a lesser control over the outcome. If I am working for a patient and his insurance covers only if he is in the hospital, then it is best for him to be in the hospital. His interests take precedence over community interests or insurance company interest. Most doctors have always done this—put the interest of their patients first. Only recently are we beginning to think in terms of "what's best for the community" and about delivering health care services to whole groups of non-patients. I am not at all sure this is progress.

The Cottage

Having a doctor of one's own is the first step in using the present health care system. My own prejudice would dictate a family physician for this slot as a matter of efficiency, but more limited specialists, practicing in mixed groups, can also act as primary physicians. When one signs up with a primary physician, he is also signing up for his system package; his hospitals, his consultants, his office staff, and his knowledge of community resources. This is our system. Its basis is individual contract (cottage) units and although it is not under a single roof like a factory, it is a system nevertheless.

The Factory

Primary health care—in fact, all health care—involves a personal relationship between a physician and his patient. Institutions and even large

*Minneapolis, Minnesota.

groups of doctors are not well known for this personal touch. They often do try, but the personal "caring for" that is the heart of our present cottage system is exactly what a more rigid system loses in the efficiencies of its organization. This "caring for" is given by people (not just doctors) who care.

Any system that proposes to deliver health care to large groups of people becomes involved with consumers and providers, efficiency, resource allocation, market penetration, and cost effectiveness. These concerns are a generation removed from the individual contract for care that presently occurs between a doctor and his patient. Our cottage system delivers health care to individuals and has never learned to put community interest and efficiency ahead of the individual.

Franchising health care and treating the health care systems as a public utility may be good for the communities, but the individual becomes lost in the concern for the greatest good for the greatest number. For the future, we have to decide between a more comprehensive and efficient system that is of necessity more impersonal, or modifications of the present system that would retain the personal relationships.

A traditional part of our cottage system has been a "fee for service" type of payment plan, with only the more expensive hospital care prepaid through various insurance plans. The danger in a fee for service practice is that the doctor gets paid for doing things. The harder he works, the more money he earns. For many people (and doctors are people) this is a powerful incentive. If the doing of things becomes excessive, it is called *over* utilization and harms the pocketbook of the patient. The danger of a pre-payment plan (HMO) is that the doctor gets paid the same no matter how much he works. For many people (and doctors are people) this is a powerful incentive not to do things. In medicine, not doing things is called *under* utilization and can harm the patient. Keeping a patient out of the hospital is only a good thing if he doesn't need to be in the hospital. Farmers shouldn't get paid for not growing corn and doctors shouldn't get paid for not caring for people.

Cottages Are Cost Effective

A HEW study reported in MEDICAL ECONOMICS in June, 1973, showed that the average cost of a visit to a doctor's office was $9.59, to an HMO was $18.07, to a community clinic was $21.16 and to an O.E.O. federally subsidized clinic the cost was $23.68. In 1973, the median office call charge for all Twin City physicians was $8.00.[1] This includes the doctor, the room and the usual supplies. In a fairly typical suburban hospital emergency room the physician charge was $13.75, the room charge $10.00 and supplies may be extra. Charges for Xrays, laboratory and various other procedures show similar differences if you compare the office with the hospital emergency room. A doctor's office is the most efficient, economical place to get primary care.

Like everything else, doctor's charges are going up—but not fast enough to keep pace with expenses. A Library of Congress research report[3] released last year showed that the median net income for physicians was the same in 1973 as it was in 1972 and 1971; and was actually $300 less than in 1970.

Minnesota physician's charges also compare favorably with national averages. We were low to start with and have risen less than the rest of the country. A Northland study[4] published in 1973 showed that the 1971 Minnesota fees for office and hospital care was less than the 1969 national average.

To make the best use of this local bargain in health care, it is necessary to have a primary physician one can call his own. This is the essential first step in utilizing our "cottage" system. At least in this seven-county metropolitan area, most people *do* have a doctor and *are* satisfied with the present system of care. A metropolitan poll done by the Minneapolis Star in October, 1973, showed that over 85% of those questioned had a primary physician. It also showed that over 88% were satisfied with the health care they were getting and that health care ranked last (tenth place) when concerns of Minnesotans were ranked in order of importance.

A 1975 survey[2] of Senior Citizens living in five areas of Minneapolis showed that 89-95% (depending on the neighborhood) had a regular physician for their care and that 74-93% rated their care as good to excellent. We are proud of our present system, but it can be improved and we do want to reach that minority who do not have a doctor and so are dissatisfied with the status quo. We must continue to explore alternate systems.

Doctor Surplus

In 1974, the Hennepin County Medical Society had 1,698 members. In the 1970 census, the Hennepin County population was 960,080. This gives us an overall ratio of one doctor for every 565 patients. Almost half of these doctors (792), are pediatricians (81), internists (226), family doctors (270), obstetricians (105) and general surgeons (110), all of whom can be expected to serve as primary care physicians.

To be realistic, though, we should subtract those doctors who list a subspecialty as they would contribute only minimally to first contact care. There are 134 of these subspecialists; 23 pediatricians, 91 internists, and 20 surgeons. Subtracting the 134 subspecialists from the 792 primary physician possibilities leaves us with 658 physicians who presumably devote most of their time to primary care.

Most of the surgeons do not devote *most* of their time to primary care, but at least a part of the day of a general surgeon is devoted to primary type medicine in the office. To balance this somewhat nebulous inclusion of surgeons in with primary care physicians, I haven't included any of the residents (808) or staff physicians (128) at the University, Veterans and General Hospitals. Staff and residents in the five primary care categories give a great deal of first contact care in the teaching program clinics located in various parts of the country.

In balance, then, I think that our earlier figure of 658 is a fair and honest guesstimate of the number of primary care physicians in Hennepin County. Now the harder question of, "How many do we need?"

The average number of doctor visits per person per year is stated by the U.S. Census Bureau to be about 4.5. The average urban family physician sees 153.8 patients per week during a 48.2 week work year as noted in the AMA profile of medical practice, 1971. Based on these figures, we need 582 primary physicians in Hennepin County.

The Directory of Primary Physicians published this year by the Hennepin County Medical Society and the Coalition of Health Care lists 596 primary care physicians practicing in Hennepin County.

I can't speak to the accuracy of these national averages, but I know that they are a long way from my own practice experience. In our office, we have 4,707 active patients (seen at least once in the last five years). Last year we had 8,480 patient visits (176 per week for a 48 week year). Thus our average number of doctor visits per patient per year is 1.8, not 4.5 as in the Bureau of Census figures. Based on this ratio, we would need only 204 primary physicians in Hennepin County. Other methods of calculation will yield need estimates falling somewhere between these two figures; but no matter how you calculate it we end up with a slight surplus of primary care physicians in Hennepin County and a larger surplus of secondary care subspecialists.

Doctor Distribution

However, leaving a surplus of doctors and even an optimal ratio of primary physicians doesn't take distribution into account. We really don't know how close the nearest doctor should be, except that when you are sick, the nearer the better. Ten minutes by car is not far but not everyone has a car. Thirty minutes by bus wouldn't be bad, but sick people sometimes can't take buses. A fifteen minute round trip by ambulance would seem reasonable and for an urban area this would mean a seven to eight mile radius. By this standard, a single office at the corner of Wayzata Boulevard and Highway 100 would cover all of Minneapolis.

The other extreme is a patient who told me she couldn't get a doctor because she lived in a part of the city where she was afraid to walk across the street to the clinic. Now this may be a problem, but we can't make it a part of the problem that our medical system has to try to solve.

Summary

Medical care given in our midwest area ranks with the best in the nation. People come here from all over the world to get medical care. Even including the higher priced large Clinic facilities, our charges are lower than most areas of the nation. We are proud of the care we give our patients and most patients are pleased with their care. Our present system is not perfect but most likely future systems will also be imperfect. We must be careful not to compromise the care to the 85% who are well cared for as we strive to improve the care to the 15% who are dissatisfied and feel that the present system does not answer to their needs.

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1. Blue Cross-Blue Shield study reported in Minneapolis Tribune, 19 April, 1974.
2. Senior Citizen Health Research Project, Hennepin County Health Coalition, April, 1975.
3. AMA News, 16 September, 1974.
4. Northlands Regional Medical Programs, "A Profile of Medical Practice in Minnesota," June, 1973.

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INTERNIST, with or without subspecialty interest (allergy especially helpful), to join 2-man group in Ashland, WI. Located on Lake Superior, this progressive, burgeoning medical community serves 120,000 drawing area and boasts a new 130 bed JCAH hospital, which includes a 5-bed ICU/CCU and a 20-bed mental health wing to open this fall. Present staff consists of 9 generalists and 17 specialists, only 2 of whom are internists. Applicant should be board certified or eligible, and willing to practice general internal medicine. Space presently available in Internal Medicine suite designed for 3 and located in Medical Center Offices, a modern complex in lower level of hospital. Progressive school system, new high school, vocational school and 4-yr. college. Please mail C. V. to: Philip H. Soucheray, M.D., 2101 Beaser Avenue, Ashland, WI 54806 or call collect after 6 PM: John Kluge, M.D., 715-682-4413.

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WANTED—Family Practitioner: To join two other physicians in Hastings, Minnesota. Community of 13,000. 30 mi. from the Twin Cities. Active hospital and Clinic practice. View partnership in one year. Write: Hugh MacMenamin, M.D. Mississippi Valley Clinic, Suite 3, Hastings, Minnesota 55033.

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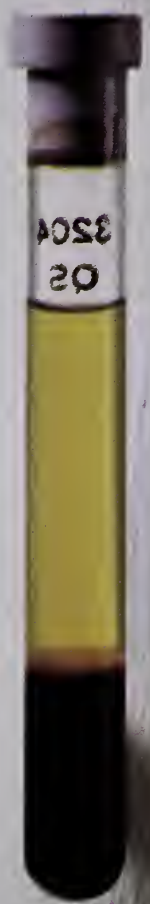
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An agent for low density lipoproteins, "type II hyperlipidemia," in euthyroid, non-cardiac patients.

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See reverse side for full prescribing information

Choloxin® (sodium dextrothyroxine)

The Lipid-Lowering Agent with Once-A-Day Dosage

Four strengths . . . 1, 2, 4, and 6 mg. . . . are available making the scored tablet regimen a flexible dosage system. And, for most patients, CHOLOXIN tablets offer once-a-day dosage.

AN IMPORTANT NOTE:
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CHOLOXIN® (sodium dextrothyroxine) Single-Tablet-A-Day Dosage Schedules

See prescribing information in package insert reproduced below.

	Starting Dosage	Increased Monthly by	Usual Maintenance	Maximal Recommended
Adult Hypercholesterolemic	1.0-2.0 mg.	1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac	0.5-1.0 mg.	1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as D-3,5,3′,5′-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

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Fall Seminar Offered

Saturday, November 8th, 1975, the Subcommittee on Alcohol and Other Chemical Dependencies is presenting a one-day Seminar entitled "Handling Chemical Dependency problems in the office practice." There will be several short lectures dealing with prevention, early intervention, treatability and referral of clients you suspect to have drug related problems. All Physicians and spouses are invited to attend. The Seminar will be held at the Radisson South, 7800 Normandale Blvd. Registration is $15.00 for Physician and $5.00 for the spouse to include luncheon. An added attraction for those interested, is November 9th, the Minnesota Vikings meet Atlanta in the Met Stadium at 1:00 p.m. All hotel arrangements must be made directly with the hotel. To call the Radisson South, dial (612) 835-7800.

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Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.
Contraindications: Patients with known hypersensitivity to the drug.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.
Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.
Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety and tension, 5 or 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
Supplied: Librium® (chlordiazepoxide HCl) *Capsules*, 5 mg, 10 mg and 25 mg—bottles of 100 and 500; Tel-E-Dose® packages of 100, available in trays of 4 reverse-numbered boxes of 25, and in boxes containing 10 strips of 10; Prescription Paks of 50, available singly and in trays of 10. Libritabs® (chlordiazepoxide) *Tablets*, 5 mg, 10 mg and 25 mg—bottles of 100 and 500. With respect to clinical activity, capsules and tablets are indistinguishable.

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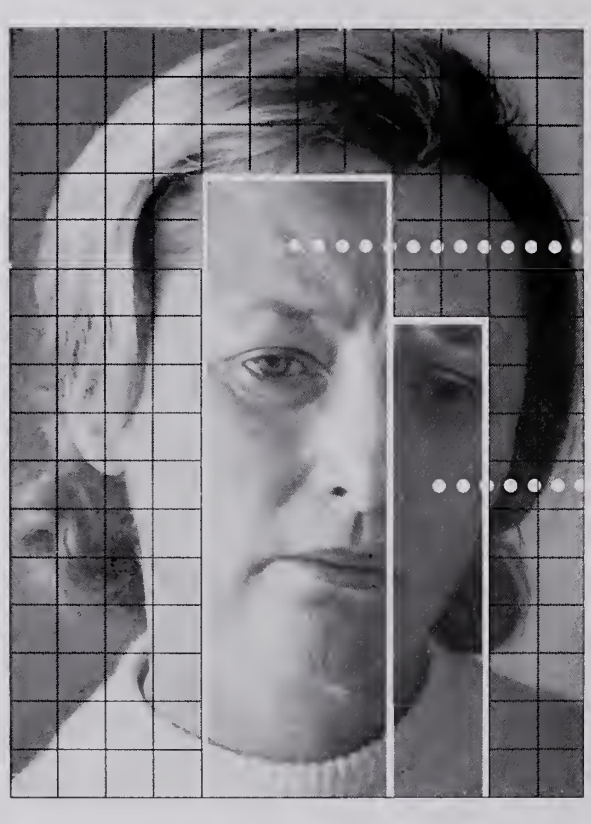
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John A. Matthews, M.D.

DECEMBER 1975

Both often



Predominant psychoneurotic anxiety

Associated depressive symptoms

Before prescribing, please consult complete product information, a summary of which follows:

Indications: Tension and anxiety states; somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

Contraindicated: Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

Warnings: Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in fr and/or severity of grand mal seizu require increased dosage of stand convulsant medication; abrupt wit may be associated with temporary crease in frequency and/or severit seizures. Advise against simultane gestion of alcohol and other CNS d sants. Withdrawal symptoms (simi those with barbiturates and alcoh occurred following abrupt disconti (convulsions, tremor, abdominal a cle cramps, vomiting and sweatin addiction-prone individuals under

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in the patient within a few days rather than in a week or two, although it may take longer in some patients. In addition, Valium (diazepam) is generally well tolerated; as with most CNS-acting agents, caution patients against hazardous occupations requiring complete mental alertness.

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2-mg, 5-mg, 10-mg scored tablets

in psychoneurotic
anxiety states
with associated
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Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or oversedation.

Side Effects: Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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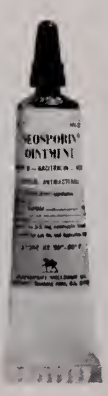
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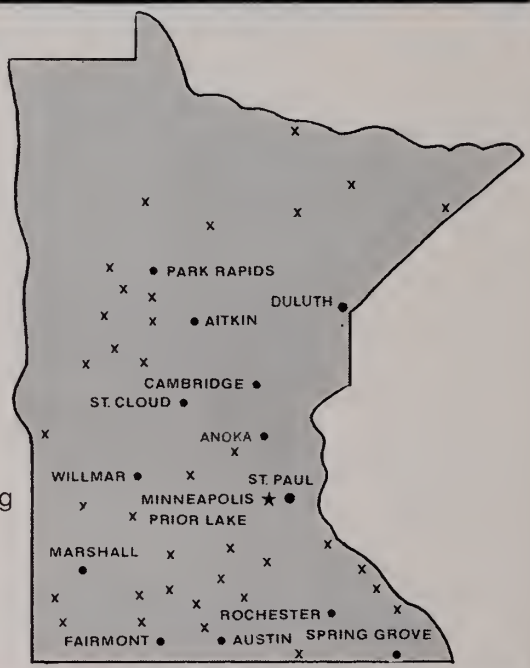
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President's Letter



The Provider

Bureaucracy in government has not only spawned a host of mind boggling, alphabet soup designations for laws, programs, bureaus, agencies and departments but it has, almost of necessity, developed descriptive language of its own that gradually comes into common use. This is particularly true in health legislation. For example, only a few years ago, terms such as provider agreements, ambulatory health care facility, extended care, concurrent review, and health systems agency were either not used or would have required detailed explanation if used. Unfortunately, some of this "accepted" terminology is used loosely, and only when the definitions or regulations are read do the restrictions become clear. The use of the term "provider" is particularly important to physicians.

Who is a "provider" of health services? The obvious answer given immediately is that it is the physician. But as more consideration is given, it becomes obvious that many others provide or are involved in giving health services. The hospitals, extended care facilities, and nursing homes are institutional providers. Those in the health related sciences and allied health professions in clinics, physician offices, and health care institutions are providers even though some have a very limited or secondary provider function. Yet in the broad sense and in almost all legislation now being written, the term "provider" includes the entire group. Who, then, becomes the advocate of the physician and our patients?

In these days of ascendency of consumerism, it is of great concern to understand that when representation on committees, councils, boards and agencies in health legislation is spelled out the consumer is frequently given a majority representation and the providers a minority—and if the numbers of types of providers is designated, the physician provider usually becomes a minority of the minority. Restricted to such a position, the physicians must exert every effort to take full advantage of even such a limited role and participate to the maximum degree possible. As the leaders of the health care team, the providers, we must seek even greater involvement.

G. Roy Diessner, M.D.
President
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christmas is green

well doctors my boss
the editor has done it again
he has bugged out and left me
the duty of filling this page
i have this message for you
christmas is green
and not for the reason you think
it is green because it is green
this is simply a matter of fact
it is ridiculous to ask why
oh i know some say it is white
some even say it is blue
while others claim it is red
these people are wrong
white is new year s day
blue is reserved for columbus day
and the fourth of july is red
a hot red
a glorious red
a swinging beautiful sunset red
what about brown
could christmas be brown
no brown is thanksgiving
thanksgiving looks smells and sounds brown
a glowing lush golden brown
of course labor day is gray
what other color could it be
it sounds correct and it is correct
besides there is no other holiday
that is remotely gray
not washington s birthday which is purple
or lincoln s birthday which unfortunately is black
and so all holidays are accounted for
except easter and memorial day
easter as everybody knows is yellow
a light yellow almost a white yellow
some uninformed people say easter is pink
but these people are uninformed

and what about memorial day
undoubtedly that day is orchid
a mixture of sadness and gladness
and red and white and blue
so orchid memorial day is
by logical exclusion
that leaves green for christmas
what does all of this have to do
with minnesota medicine
nothing at all
but it has everything to do
with faith and hope
and colors and celebrations
and imagination
after all that is what
christmas is all about

minny

Annual Meeting

All I Want for Christmas . . .

I don't want to interrupt busy holiday schedules with lengthy enticements to come to CME '76 in Rochester. I do, however, want to take time to introduce this year's Scientific Assembly team, a team that has not only planned a current and vital program, but exceeded all expectations for securing program participants, employing innovative audio-visual techniques, and providing tremendous subject variety. Thanks to the Subcommittee's unsurpassed accomplishments, everything I wanted for Annual Meeting by next spring, I received by December.. 'Tis truly the season to be jolly!

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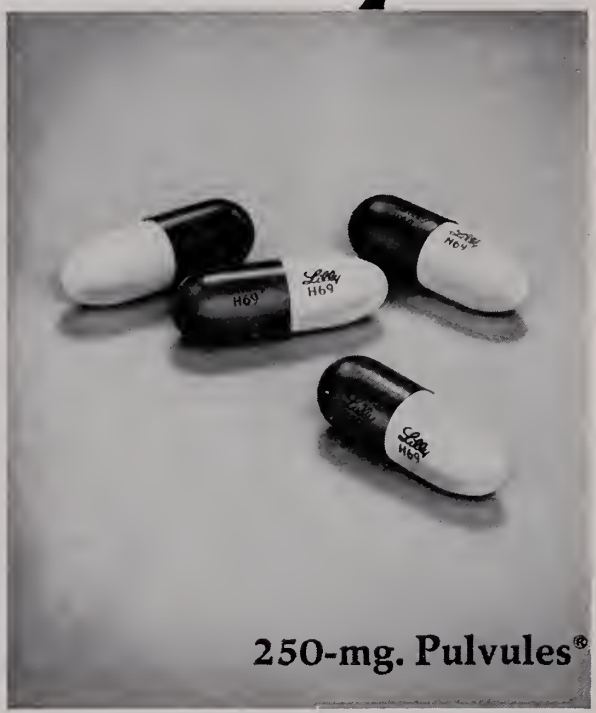
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Allergic Contact Dermatitis from Footwear

Shoe Dermatitis in 42 Patients

MARK V. DAHL, M.D.*

Patients with suspected allergic contact dermatitis to footwear were patch tested to a battery of chemicals used in leather, vinyl plastics, adhesives, insoles, and other shoe components. Allergic contact dermatitis was documented in 42 patients and the specific allergen or allergens identified in 33. The most common allergens were mercaptobenzothiazole[13] and tetramethylthiuram[9] used in rubber adhesives. Phenolic resins[8] and the leather tanning agents chrome[9] and formaldehyde[2] were also identified as allergens. No allergy to vegetable tanning agents or glutaraldehyde was documented. Colorants may also produce allergic contact dermatitis. Allergic contact dermatitis to components of footwear is common. Since appropriate substitution may allow cure, patch testing of most patients with recalcitrant foot dermatitis is often indicated. Patch testing provides a reproducible method for detecting allergy and specifying appropriate substitution therapy.

FOOT DERMATITIS is common. The differential diagnosis includes tinea pedis, atopic dermatitis, psoriasis, dyshidrosis, gram-negative bacterial infection, erythrasma, keratoderma, mechanical and chemical irritant dermatitis, and allergic contact dermatitis.

Allergic contact dermatitis results when a person develops hypersensitivity to one or more chemicals contacting the skin. Poison ivy (Rhus) dermatitis is the best known example.

There may be allergic contact sensitization to a myriad of chemicals including metals, cosmetics, preservatives, and ingredients of various topical medications. Similarly, sensitization and subsequent allergic contact dermatitis may result from chemicals in shoes or other footwear.

The purpose of this report is to document the contact allergens among a group of patients with allergic contact dermatitis to footwear.

Methods

Fifty-nine patients who presented with a persistent foot dermatitis for which no cause could be readily assigned were studied. All patients had negative KOH examination for fungi.

*Assistant Professor of Dermatology, University of Minnesota Hospitals, Minneapolis, Minnesota.

Reprint requests to: Department of Dermatology, Box 98 Mayo, University of Minnesota Hospitals, Minneapolis, Minnesota 55455.

Patch tests were performed as previously described.[1,2] Briefly, various suspected allergens were incorporated in suitable concentration in an ointment base, usually petrolatum. The concentrations used were either those listed by Fisher[3] or determined according to standard methods.[3] At the concentration used, the chemical was not irritating to normal skin of at least 10 control subjects under conditions of the patch test. Small amounts of prepared allergens were applied with tape to pa-



Fig. 1—Allergic contact dermatitis from footwear may begin as dermatitis of the dorsum of the feet with sparing of skin between the toes.

TABLE 1
Chemicals and Concentrations used for Patch Testing Patients with Suspected Shoe Dermatitis. Unless Specified, the Vehicle is Petrolatum Alba

Resins
- Arofene 8840
- Cumar w2 ½, p-coumarone indene 2%
- Pentalyn H 2%
- Beckamine 27580 2%
- Vultac #3, Alkyl phenol sulfide 2%
- Krumbhaar 254, phenylphenol formaldehyde 2%
- Stabelite 49453, Diphenyl propylenediamine 1%
- Beckamine 49464, polymeric styrenated phenol 2%
- Zerex resin, Zinc resinate 2%
- Mohawk, Alicyclic ketane resin 2%
- Varcum 875, phenolic resin 2%
- Pentalyn K, 2%
- CAO-6, 1%
- CAO-14, 1%
- Stabelite 49451, Diphenyl ethylenediamine 1%
- Durez 175, phenol formaldehyde 2%
- SP-103, p-tert-butyl-phenol formaldehyde 2%
- Chlorowax 70, chlorinated paraffin resin 1%
- SP-560, Terpene phenolic resin 1%
- Melamine formaldehyde 10%
- p-tert-butyl-phenol 1%

Rubber Components
- Mercaptobenzothiazole 1%
- Tetramethylthiuram 1%
- Tetraethylthiuram 1%
- Diphenylquanidine 1%
- Zinc diethyl-dithiocarbamate 1%

Dyes
- Wood Orange A 1%
- paraphenylenediamine 1%
- Calcocid Orange 2G 1%
- Calcozine Black 1%
- Nigrosine B 1%
- Oil yellow I 0.5%
- Solvent Red 2G 0.5%
- Disperse Orange 0.5%
- Leather Brown 5RTA 0.5%
- Euchrysine GGA 0.5%
- Bismark Brown 1%
- Bismark Brown R 1%
- New Blue RS concentrate 1%

Plastics & Epoxies
- Butylated Bisphenol A 1% in acetone
- Methylmethacrylate 25% in olive oil
- Triethylene tetramine 0.5%
- Epon 812 1%

Miscellaneous
- Sanowhite crystals 1%
- Dimethylol urea formaldehyde 10%

Tanning Agents
- Chrome 0.5% (as potassium dichromate)
- Glutaraldehyde 1% aq. sol.
- Formalin 2% aq. sol.
- Chestnut 1%
- Wattle 1%
- Quebracho 1%
- Mirabilum 1%
- Crotan 5%
- Tanolin R 0.1%

Preservatives
- o-nitrophenol 1%
- pentachlorophenol 1%
- copper 8-quinolinolate 1%

tients' backs, under occlusion with an aluminum foil patch test unit (Al-test). After 48 hours, all patches were removed. Sensitivity was documented when the skin was indurated and erythematous at a patch test site. Readings were made 48, 72 and 96 hours after application of patch tests.

All patients were tested with a standard screen of 22 allergens. If relevant allergic contact dermatitis was not demonstrated, each patient was subsequently tested to a battery of chemicals assembled from various sources. Chemicals in this battery are listed in Table I and included known allergens in footwear, chemicals in footwear of cooperating shoe manufacturers, and chemicals obtained from various shoe resin or shoe leather suppliers, or other sources. Since new materials were added to this battery during the course of study, not all patients were tested with all substances listed in Table 1. If positive patch tests still were not obtained, the patient's shoes were dissected and each component was applied as patch tests after moistening in tap water.[4] All positive patch tests obtained by this method were repeated since false positive tests from mechanical or other irritative factors were common among patients tested to portions of shoes themselves. If allergic sensitization was documented, manufacturers were contacted and appropriate chemicals obtained for further patch testing.

Results

Fifty-nine patients with possible allergic contact dermatitis to footwear were patch tested. Allergic contact dermatitis to shoes or shoe components was demonstrated in 42. The specific allergen or allergens were identified in 33. In nine patients, patch tests to shoe portions themselves were positive, but it was not possible to identify the responsible specific allergen. Specific allergens identified in other patients are listed by group in

TABLE 2
Allergens in Shoe Dermatitis (Allergens identified in 33 of 42 patients)

Mercaptobenzothiazole	13
Tetramethylthiuram	9
Chrome	9
Phenolic Resins	8
Dyes	5
Paraphenylenediamine	5
Formalin	2
Non-phenolic resins	3
Carbamates	2
TOTAL	56

Table 2. Often, patients with shoe dermatitis were allergic to more than one chemical.

Discussion

Although shoe dermatitis may occur on any area of the foot, usually it first appears on the dorsum of the toes and foot, sparing the skin between the toes[4]. Sweat may leech chemicals out of one area of the shoe and transfer them to distant sites, so that any or all areas of the foot may be involved. Characteristically, patients have had recurrent foot dermatitis for many years and have tried numerous topical remedies.

Patch testing provides a reproducible method of documenting allergic contact dermatitis from footwear, identifying the offending antigen or antigens, and delineating appropriate substitution therapy.[5]

Common Allergens

In this series of patients, the most common allergens were components of rubber and rubber adhesives, particularly tetramethylthiuram and mercaptobenzothiazole. Because they are relatively inexpensive, durable, and resistant to moisture or mechanical stress, virtually all shoes manufactured in America today contain rubber-based adhesives. Certain sandals, and one-piece injection-molded or pour-molded shoes or boots are made without rubber adhesives, but in general do not offer a suitable alternative to most patients. Thus, specially constructed "hypoallergenic" shoes often must be prescribed for patients allergic to rubber components.

Other common allergens are chrome and formaldehyde, present in most leathers as tanning agents. Nine of 42 patients with allergic contact dermatitis to footwear had positive patch tests to potassium dichromate. Two were allergic to formalin. The dermatitis often disappeared after the patients discarded offending shoes and began to wear tennis shoes or vinyl-plastic injection-molded shoes containing no leather. Vegetable-tanned leather or glutaraldehyde-tanned leather shoes might also be acceptable substitutes. Although persons allergic to vegetable tanning agents or glutaraldehyde can develop dermatitis from glutaraldehyde or vegetable tanned leather,[6] no patients, in this series were allergic to these chemicals.

Dyes

Allergy to colorants is difficult to demonstrate.



Fig. 2—Allergic contact dermatitis of the side of the foot caused by components of a rubber adhesive. Allergic contact dermatitis should be considered in the differential diagnosis of chronic, scaling eruptions of the feet.

A multitude of dyes are currently available to leather processors and synthetic shoe manufacturers. Most currently used leather colorants are direct and acidic dye stuffs, often azo dyes. Many colorants are mixtures of individual dyes. Allergy to colorants was suspected when patients developed positive patch test reactions to paraphenylenediamine, or individual screening dyes, or both.

Treatment of patients with allergic contact dermatitis to colorants may be difficult, since the color of the shoe may be no clue. Cross reactions between individual azo dyes are common, and many colorants are mixtures of two or more dyes of different colors. In general, substitution of tennis shoes, deerskin, white buck or other undyed leather shoes may eliminate the dermatitis, but these alternatives often are stylistically unsatisfactory. In these patients, prospective testing to hypoallergenic components of special shoes is useful to ascertain whether a patient will be able to wear a specific shoe.

Allergic Dermatitis—A Common Cause

Allergic contact dermatitis from footwear is a relatively common cause of foot dermatitis. Sometimes the classical clinical presentation of dermatitis on the toes and dorsum of the foot makes the diagnosis obvious. In others, unusual patterns of dermatitis occur, which may not immediately suggest an allergic contact etiology. Allergic contact dermatitis to footwear is also found as an addition-

al complicating factor in some patients with other forms of dermatitis, such as athletes' foot.

Since allergic contact dermatitis to footwear is common, and since appropriate substitution of other footwear usually provides cure, patch testing may be indicated for most patients with chronic dermatitis of the feet.

Acknowledgment

The teaching, assistance, and enthusiasm of William P. Jordan, Jr., M.D., Department of Dermatology, Medical College of Virginia, Richmond, Virginia is gratefully acknowledged.

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COVER PHOTO

"22° F"

Dr. John Matthews took the cover photo from his bedroom window about 6 a.m. last February. The camera is a Miranda, and while resting the camera on the window sill, Dr. Matthews using a wide angle, 35 mm lens, caught the icicles shown.

A dabbler in photography since 1945, he spends a great deal of his spare time finding unusual subjects to photograph. He was born in South Africa, and after five years began training in radiation therapy in Scotland and then on to England after completion of his schooling. In 1961 he went to Ontario as a radiation therapist with the Ontario Cancer Foundation where he stayed until 1967. Later he came to the University of Minnesota, then to Ramsey County General Hospital and for the past five years has been running the West Bank Radiation Center in Minneapolis.

Letters to the Editor

We would like to encourage physicians to contribute to the Letters to the Editor Section. We want to hear what you have to say, what you think, why you hold certain opinions. In short, we want to make this as lively and spirited a section as possible.

The Editors

University of Minnesota
OB-GYN Department

The OB-GYN Department announces a special lecture by Julian T. Parer, M.D., Ph.D., Assistant Professor, Obstetrics and Gynecology, University of California, San Francisco, entitled "Clinical Implications of Normal and Impaired Placental Exchange", will be presented on Friday, December 12, 1975, at 1:15 P.M. in Room D520 of the University of Minnesota Hospitals. Merrell-National Laboratories is the sponsor.

Vitamins and Cancer

ATHANASIOS THEOLOGIDES, M.D., PH.D.*

Patients with advanced cancer frequently develop vitamin deficiencies. Vitamins should be supplemented because there is no convincing evidence that they accelerate the cancer growth.

Advanced cancer and drugs used to manage cancer may interfere with the proper nutrition of the patient and may cause vitamin deficiencies. Leevy and co-workers[1] studying the incidence and significance of hypovitaminemia in a randomly selected municipal hospital population, observed all nine patients with neoplastic disease had low circulating levels of one or more vitamins.

In clinical medicine administering multi-vitamin preparations to debilitated, anorectic cancer patients is common. Giving large parenteral doses of a single vitamin or "high potency" multi-vitamin preparations is also practiced frequently. Is giving large doses of various vitamins innocuous to the cancer patient? Can vitamins stimulate the rate of tumor growth and accelerate the course of the disease?

A few reports exist in the literature of an apparent detrimental effect of vitamins on the course of the malignant disease. Heinle and Welch[2] reported that administration of a form of folic acid, pteroylglutamic acid (PGA) to three patients with chronic myeloid leukemia was attended by rapid hematologic and clinical relapse in each instance. In one of these patients hematologic improvement accompanied the withdrawal of PGA on two occasions.

Recently Chauvergne and co-workers[3] observed that B 12 stimulated tumor growth. They studied patients with a variety of tumors such as adenocarcinoma of the breast, rectum and thyroid, carcinoma of the larynx, reticuloendothelial malignancies and others. The authors cautioned about the interpretation of their observations and emphasized the possibility of a fortuitous coincidence of the rapid evolution of cancer with the administration of vitamin B 12.

Is there any relationship between vitamins and cancer? Is there any concrete evidence that high doses of one or multiple vitamins stimulated the growth of animal and human tumors?

Animal Studies

The discovery of vitamins and the recognition of their role on the integrity and growth of various tissues led to the investigation of their potential relations to genesis and growth of cancer. Initially the vitamin content and requirement of spontaneous and induced animal tumors were compared to those of normal tissues. It was expected to find major qualitative and quantitative differences and use these differences to control experimental and clinical cancers by means of therapeutic vitamin deficiencies and excesses. However, tumors were found to have higher, others lower, and others similar vitamin content to comparable or unrelated normal tissues.

Moderate to severe vitamin deficient diets were shown to inhibit the rate of growth of a variety of induced and spontaneous animal tumors.[4] Such effect was observed not only on established tumors but also on the development of animal cancers. Virtually all the known vitamins have been studied. But the inhibitory effect usually was achieved with a great adverse effect on the well being and growth of the host.

As far as high vitamin doses stimulating the rate of growth of certain experimental tumors, there is only fragmentary and controversial evidence available. Oleson and Little[5] demonstrated that increasing doses of vitamin B 12 and folic acid increased the incidence and size of Rous tumor implants in chicks. When pteroylglutamic acid and vitamin B 12 were given together the tumors came up earlier and attained greater size

*Professor of Medicine, University of Minnesota Medical Center, Minneapolis, Minnesota.

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than with corresponding levels of either vitamin alone. Thompson and Voegtlin[4] have noted in a population of rats an apparent growth promoting action of both excess biotin and riboflavin added either singly or in combination upon actively regressing hepatoma 31. Brunschwig[6] reported that an excess of vitamin C appeared to stimulate mildly the growth of certain transplantable tumors. But such stimulatory action could not be consistently elicited under apparently uniform experimental conditions.

After a critical review of the literature Greenstein[7] concurred with the generally held viewpoint that above a minimum level any variations in dietary vitamin content has little or no effect on the growth of animal tumors.

Human Studies

For human cancers there were claims[8] that diets rich in certain vitamins stimulated growth of tumors and that excesses of certain vitamins had a growth promoting effect. However, these claims were based on conjectural evidence and not on well controlled clinical observations. Nevertheless, some investigators recommended and tried vitamin deficient diets for cancer patients. Even a diet that was almost vitamin-free was tried in cancer patients but apparently without encouraging results.[9] A vitamin deficient diet should not be recommended for the cancer patient and has no place in the management of cancer.

The introduction of vitamin analogues raised hopes for significant antitumor effect with less toxicity on the host. Although a great number of analogues have been tested, at present only the folic acid antagonists are useful clinically, inducing remission in certain acute leukemias, metastatic choriocarcinoma and a few other cancers.

There is no convincing clinical evidence that high doses of vitamins accelerate human cancer growth, with possibly one exception, the possible occurrence of an accelerated course in certain leukemias following the administration of folic acid.[2] This very possibility actually led to the synthesis of the folic acid antagonists.[10] Nevertheless, Beck has administrated folic acid to many patients with chronic leukemia and acute granulocytic or myelomonocytic leukemia without evidence of clinical exacerbation.[11]

On the other hand a high incidence of folic acid deficiency in patients with a large variety of neoplastic diseases has been documented based on serum folate levels, folate clearance, abnormal FIGLU excretion and megaloblastic anemia.[12-14] Correction of this deficiency with the administration of folic acid has beneficial effect on the anemia.[13] But does it accelerate the rate of tumor growth also? Physicians have been reluctant to administer folic acid in leukemias and solid tumor fearing potential stimulation of the malignant growth. Beck believes that folic acid therapy does not accelerate malignancies that are not benefited by antifolatc therapy.[11] However, high doses of methotrexate, a folate analogue, can induce partial regression in a considerable number of malignancies. Is folate therapy contraindicated in these tumors? The answer is probably no. Citrovorum factor (folinic acid) is given to decrease methotrexate toxicity apparently without minimizing the anti-tumor effect.

Patients with advanced cancer are debilitated and have several complications leading to nutritional and dietary problems and vitamin deficiencies, particularly of the vitamin B complex. These patients should be watched and vitamin deficiency should be anticipated. The appropriate vitamin should be supplemented without the fear that vitamin replacement will accelerate the growth of their tumor, by "feeding the cancer." However, there is no reason to believe that a "high potency" multi-vitamin preparation or high doses of single vitamins are of any beneficial effect once the daily vitamin requirements are met. The daily requirements for most vitamins in the uncomplicated cancer patient probably are not markedly different from the normal individual or from patients with other chronic debilitating disease.

Massive doses of vitamins for the treatment of cancer have been used in two areas; vitamin A for oral leukoplakia with beneficial effects on this precancerous lesion and vitamin B 12 in the treatment of neuroblastoma with questionable effects.

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4-14. Will be found on page 881.

Intracranial Ependymomas

Report of a Case and Literature Review

FREDERICK M. VINCENT, M.D.*

Intracranial ependymomas account for 2% to 9% of all central nervous system gliomas and thus are considered to be rare tumors. They most commonly present during the first two decades of life, and are very rarely seen past the age of 50. Spread to the cerebellar hemispheres and to the cerebellopontine angle is considered to be quite rare. The case report of an elderly man with a fourth ventricular ependymoma that spread to both the cerebellar hemispheres and the cerebellopontine angle is reported, and the literature is reviewed.

THE PURPOSE OF this paper is to present an interesting case of an intracranial ependymoma, and to review the literature on this subject.

Case Report

(First admission)

A 62-year-old white man was admitted to St. Luke's Hospital with the history of right sided ataxia of gait, and intermittent diplopia noted on right lateral gaze, of three to four weeks duration. A week prior to admission the symptoms had increased in severity so that the patient had become afraid to drive his automobile because of the diplopia. He gave no history of associated headache, vertigo, tinnitus, nausea, vomiting, syncope, trauma, or other neurological symptoms. General review of systems and family history was non-contributory. Past medical history revealed that in 1952 the patient underwent a left hemicolectomy for adenocarcinoma of the descending colon.

General Physical Examination

The patient was well developed and overweight. He was in no acute distress, nor appeared to be chronically ill. The blood pressure was 142/94, pulse 76 per minute, and respirations 18/minute. The healed left lower quadrant surgical incision was the only abnormality noted during the physical examination.

Neurologic Examination

The patient was alert and oriented. Extraocular muscle movements were full. Both direct and consensual pupillary reflexes were equal and brisk. The optic discs were flat and spontaneous venous pulsations were present. Corneal reflexes were symmetrical. Horizontal nystagmus was present, with the rapid movement to the right, and the nystagmus increased in amplitude on right lateral gaze. The remainder of the cranial nerves were grossly intact. The sensory examination was non-contributory. Motor strength was symmetrical with no evidence of fasciculations or paresis. Deep tendon reflexes were asymmetrical, with the right side slightly hyperactive as compared to the left. There were no Babinski, snout, or palmomental reflexes. Gait was ataxic with falling to the right. The patient was unable to tandem walk, and the Romberg sign was positive, as he fell to the right. Finger-to-nose, and shin-to-heel tests revealed mild right sided ataxia. There were no other neurological abnormalities.

Laboratory Examinations

Complete blood count, blood chemistry profile, VDRL, sedimentation rate, and electrolyte levels were within normal limits. Electrocardiogram, chest roentgenogram, electroencephalogram, and Technetium^{99} brain scan were negative. Tomographic examination of the internal auditory canals revealed some asymmetry with enlargement of the right internal auditory canal, as the ampullar region was 2 mm larger than the left.

Transfemoral cerebral angiography revealed an abnormality involving the distal aspect of the right superior cerebellar artery with abrupt cutoff and absence of filling of its marginal and lateral branches. The posterior and lateral portion of the right cerebellum was noted to be hypovascular, but there was no evidence of a mass lesion in the cerebellum or brain stem. It was felt that the above findings represented a stroke syndrome involving the right superior cerebellar artery. Lumbar puncture revealed clear colorless fluid, with a protein level of 48mg/100ml, and five RBC/mm^3. Opening and closing pressures were normal.

During his hospital stay the patient complained of less diplopia and his ataxia markedly improved. He was discharged 17 days after admission.

Final Admission (Eight days later)

One to two days prior to the present admission the patient had suddenly become more ataxic, and had developed vertigo, nausea, vomiting, and posterior headaches. Neurological examination was the same as on the previous admission, except that he had a left facial nerve palsy and an absent left corneal reflex.

*St. Luke's Hospital, Duluth, Minnesota With the technical assistance of Francis A. Carmichael, III, M.D. (deceased).
Current address: Neurology, Dartmouth-Hitchcock Medical Center, Hanover, N.H.
See editorial, page 889.

A pantopaque posterior fossa myelogram was performed and revealed a defect, measuring 2½ x 1½ cm, projecting from the region of the internal auditory meatus on the left into the pool of pantopaque (Figure 1-a). The right side was interpreted as being within normal limits (Figure 1-b). Cerebrospinal fluid obtained at the time of the myelogram was bloody, with a protein level of 92mg/100ml, and 1500 RBC/mm^3.

Five days after admission a left posterior fossa craniotomy was performed. The left cerebellar hemisphere was elevated to expose the internal auditory meatus and at this level a tumor was found that was hiding the seventh and eighth cranial nerves which appeared to be lying behind the tumor. The tumor was pear-shaped with the large end of the pear sitting in the internal auditory meatus. A small portion of the stem extended up the brain stem, and did not appear to be encapsulated. Biopsy specimens were sent for frozen section and were reported as being adenocarcinoma. Because of this diagnosis the surgeon felt that further attempts at removal of the tumor were not indicated. The wound was closed and the patient sent to the Intensive Care Unit. A few hours after surgery the patient responded to his name, but he soon lapsed into a "coma vigil" and died 22 hours after craniotomy.

General Pathologic Examination

The general necropsy was non-contributory except for the following findings. The heart weighed 525 gms. 1 cm from the origin of the descending branch of the left coronary artery there was an atheromatous plaque with an associated area of hemorrhage. The occlusion of the vessel was complete and was 3 mm in length. The other coronary arteries showed only a slight amount of atherosclerosis, as did the aorta. In the area 23 cm superior to the rectum the bowel was narrowed and scarred, but free of neoplasm.

Neuropathologic Examination

There was a surgical defect in the left occipital bone. The adjacent dura mater was slightly hemorrhagic, but there was no evidence of subdural or subarachnoid hemorrhage. The brain weighed 1525 gm and was somewhat edematous. Multiple sections through the cerebrum revealed generalized ventricular dilatation. This was found to be due to an obstructing tumor two cm into the fourth ventricle from the aqueduct of Sylvius. It was papillary and arose from the ependyma. It had involved both cerebellar hemispheres, although it was mostly on the right side. It had also crossed the midline of the fourth ventricle and extended through the foramen of Luschka on the left (Figure 2). The mass measured 4.0 x 1.5 x 1.5 cm.

Microscopic Findings

Paraffin fixed biopsy tissue revealed proliferation of an epithelial type of tumor with hyperchromatic nu-

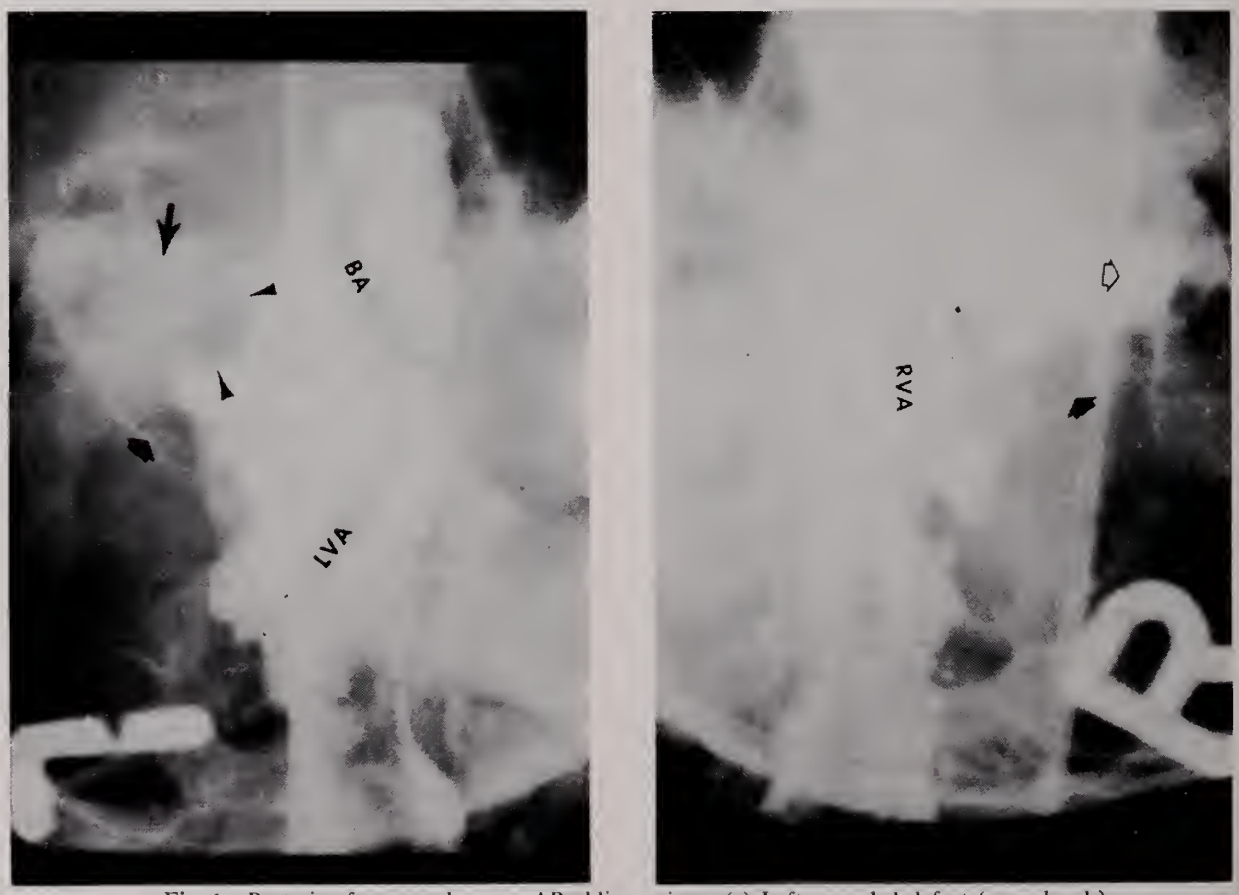


Fig. 1—Posterior fossa myelogram, AP oblique views. (a) Left, rounded defect (arrowheads) projecting into area of internal auditory meatus (large arrow). (b) Right, normal flow of pantopaque into internal auditory canal (white arrow). BA, Basilar artery; LVA, Left vertebral artery; RVA, Right vertebral artery.

clei. There was definite rosette-like configuration with some central blood vessels. These specimens were interpreted as being diagnostic of an ependymoma, grade III, not adenocarcinoma as reported on frozen section. The tumor mass from the region of the fourth ventricle was papillary, with large and hyperchromatic nuclei, and some mitotic figures. In some areas the tumor was growing in solid sheets. It was destroying brain tissue in the area of the cerebellar hemispheres, and in some of these areas there was hemorrhage.

Final Diagnosis

The immediate cause of death most likely resulted from the occlusion of the descending branch of the left coronary artery. There was an ependymoma arising from the floor of the fourth ventricle, extending into both cerebellar hemispheres and through the left foramne of Luschka into the cerebellopontine angle. Cerebral edema was present as well as beginning hydrocephalus that was secondary to obstruction of cerebrospinal fluid egress by the tumor mass.

Discussion

A review of three large series of intracranial ependymomas totaling 230 cases forms the main basis of the following discussion.[1-3]

The reported incidence of ependymoma among the intracranial gliomas ranges from 2% to 9%.[1,4,5] They are most commonly seen before the age of 50,[6] with about one-half occurring in the first two decades of life. They represent 15% of the central nervous system neoplasms in children, being the third most common tumor of the brain and spinal cord in this age group after medulloblastoma and astrocytoma.[6,7] The average age of all patients with ependymomas when first seen varies from 16.4 to 22.0 years (Table 1).

Five histologic types of ependymomas have been described:[2,3] cellular, papillary-myxopapillary, subependymoma, epithelioid, and mixed. The cellular type has been found to be the most common; in combination with other patterns it has constituted approximately three-fourths of the tumors studied by some groups.[3]

The prognosis depends in large part upon the location of the tumor. The general location of the tumor is presented in Table 1.

The most common location of supratentorial ependymomas is in the region of the third ventricle.[2] They may actually be more common in this region than is realized, for tumors in this location are frequently treated by a ventricular shunt and radiation rather than by a surgical attack on the tumor.[8] At times the majority of growth may be toward the central white matter rather than towards the ventricular cavity.[2] Those in the cerebral hemispheres are often partly or extensively cystic.[2]

Sixty to seventy percent of intracranial ependymomas are infratentorial in location.[4,9] About 90% occur in the midline of the fourth ventricle, most frequently from its floor,[2,3,9] while the remainder grow into the cerebellopontine angle from the lateral medullary velum.[5] They often



Fig. 2—Diagram of slightly oblique section through the cerebellum at the level of the foramina of Luschka and the 8th nerves. A tumor can be seen in the 4th ventricle with extension through the foramen of Luschka into the left cerebellopontine angle. There is also infiltration of tumor into the right cerebellar hemisphere.

fill the fourth ventricle and frequently project into the cisterna magna and encircle the spinal cord as they extend through the foramen magnum.[3,6] Extension about upper segments of the cervical cord is common, while spread into the cerebellopontine angle,[10] into the central canal of the spinal cord, and into and through the aqueduct of Sylvius occurs less frequently.[2] Rarely do these tumors extend predominantly into the cerebellar vermis or hemispheres.[11] Ependymomas usually infiltrate the brainstem at their points of attachment to the floor of the ventricle. They may obstruct cerebrospinal fluid flow by their position in the fourth ventricle or by extension into the aqueduct of Sylvius. Rarely they may spread to the spinal subarachnoid space, usually with associated cisternal involvement.[2] Extracranial spread to the calvarium,[12] soft tissues of the neck, lymph nodes, and internal organs has been occasionally observed following operation.[7,13]

The average duration of symptoms prior to diagnosis is from seven to 10 months.[1,2] Patients with supratentorial lesion tend to have a shorter period of symptoms (seven months),[2] more neurological deficits due to greater invasiveness of the tumor, and, therefore, a poorer prognosis[2] than those with infratentorial tumors. The latter group has a longer symptomatic period (average nine months).[2]

Headache, vomiting, diplopia, dizziness and unsteady gait have tended to be the symptoms of longest duration present before admission to the hospital.[1,2] The principal symptoms noted on admission are listed in Table 2. Other symptoms not listed in Table 2 because of their relative infrequency are:[1] nuchal rigidity, amaurosis, dysphagia, tilted head, fainting spells, paresthesias, and photophobia. The objective findings seen on admission are also listed in Table 2. The most common findings are those referable to lesions of the posterior fossa, particularly those of increased intracranial pressure.[2,14] Less commonly observed signs are drowsiness, dilated pupil, clonus, hypotonia, wide-based gait, sensory loss, 5th nerve paresis, positive Romberg, and nuchal rigidity.[1] Cases with unilateral papilledema have not been reported.[1,2]

Arteriography[3] and air-contrast studies[3,14] seem to be the preferred diagnostic procedures when a supratentorial ependymoma is suspected. However, computerized axial tomography may obviate the need for air-contrast studies. The single most useful contrast study leading to the diagnosis of posterior fossa ependymoma is pantopaque cisternography.[3]

Generally ependymomas cannot be totally removed at the time of operation.[6] Those in the fourth ventricle are exceedingly hard to excise because of their infiltrative nature, and because their blood supply is from those vessels that supply the pons and medulla.[6] The alternative is partial removal or suboccipital decompression.[6]

TABLE 1
Comparative Data on Three Series of Intracranial Ependymomas

Source	Barone & Elvidge[1]	Kricheff et al.[2]	Fokes & Earle[3]
No. cases	47	70	113
Age (yrs-			
av (all)	22	16.4	21.1
range	0.7-64	0.3-66	0.12-64
av ST	21.3	18.8	27.8
av IT	23.1	15.4	18.7
Sex (all)	64% F	51% M	....
ST	....	61% F	....
IT	....	57% M	....
Location			
ST	48%(23)	26%(18)	26%(32)
IT	52%(24)	74%(52)	74%(52)
Symptoms			
range	6.0-36 mo	0.5-36 mo	....
av ST	....	7 mo	....
av IT	....	9 mo	....

ST—supratentorial
IT—infratentorial

TABLE 2
Principal Symptoms and Signs of a Group of Patients* with Intracranial Ependymomas[1]

Symptom	% of cases	Signs	% of cases
Headache	85	Papilledema	83
		bilateral	79
Vomiting	46	unequal	4
Diplopia	27	Nystagmus	45
Decreased		Cerebellar	
vision	23	signs	26
Blurred		Extensor plantar	
vision	23	response	23
		unilateral	21
Unsteady gait	19	Hemiparesis	23
Dizziness	17	Ataxia	21
Drowsiness	17	Increased deep	
		tendon reflexes	17
Nausea	13	Sixth nerve palsy	15
		unilateral	9
		bilateral	6
Weak leg	8	Decreased vision	13
		unilateral	2
		bilateral	11
Episodes of			
syncope	8	Facial paresis	9

*47 cases.

It is usually best to excise enough tumor so as to prevent the blockage of the cerebrospinal fluid pathways.[6] The reported operative mortality in cases of ependymomas is about 20%.[2] It is higher in posterior fossa lesions than in supratentorial lesions.[2]

It seems that the treatment of choice is the removal of as much tumor as possible, followed by radiation therapy to the affected site.[2,6] 50-75% of the survivors have good functional survival.[2,15] Over fifty percent of deaths are caused by local recurrence.[6]

The case reported in the present article is interesting because a rare type of intracranial neoplasm that typically occurs in the second decade of life presented in a man who was in his seventh decade. This ependymoma caused both cerebellar and cerebellopontine angle signs, both uncommon sites for spread of an uncommon tumor.

Summary

The case of a fourth ventricle ependymoma with spread to both cerebellar hemispheres and the left cerebellopontine angle is reported.

The literature on intracranial ependymomas is reviewed. The tumor is most frequently found in the posterior fossa, originating usually from the floor of the fourth ventricle, and are rare after the fifth decade of life. Supratentorial tumors are more invasive and have a poorer prognosis because of this invasiveness. Pantopaque cisternography is the diagnostic procedure of choice in patients with infratentorial ependymomas, while arteriography, air-contrast studies and, computerized axial tomography are recommended in supratentorial lesions.

The treatment of choice is the surgical removal of as much of the tumor as possible, followed by irradiation.

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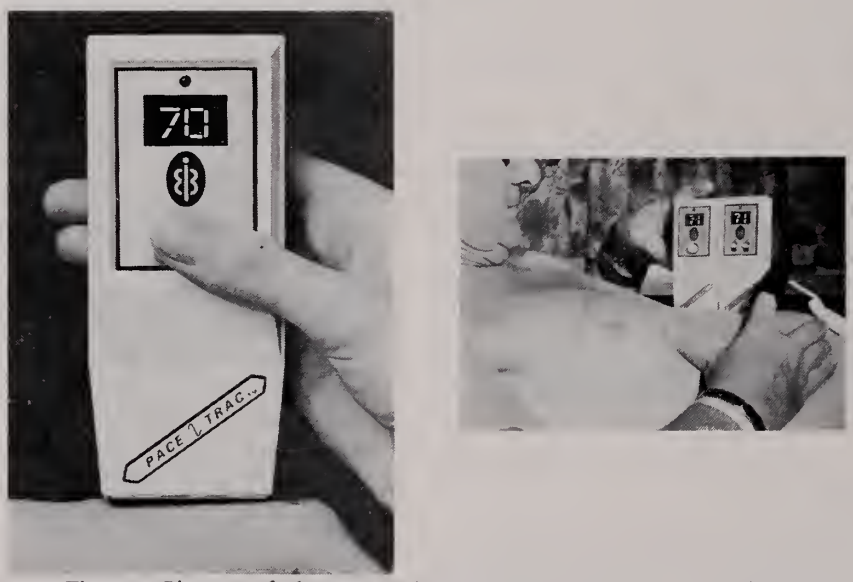
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Adverse reactions: Atropine effects include dryness of skin and mucous membranes, flushing, hyperthermia, tachycardia and urinary retention. Other side effects with Lomotil include nausea, sedation, vomiting, swelling of the gums, abdominal discomfort, respiratory depression, numbness of the extremities, headache, dizziness, depression, malaise, drowsiness, coma, lethargy, anorexia, restlessness, euphoria, pruritus, angioneurotic edema, giant urticaria, paralytic ileus, and toxic megacolon.

Dosage and administration: ***Lomotil is contraindicated in children less than 2 years old.*** Use only Lomotil liquid for children 2 to 12 years old. For ages 2 to 5 years, 4 ml. (2 mg.) t.i.d.; 5 to 8 years, 4 ml. (2 mg.) q.i.d.; 8 to 12 years, 4 ml. (2 mg.) 5 times daily; adults, two tablets (5 mg.) t.i.d. to two tablets (5 mg.) q.i.d. or two regular teaspoonfuls (10 ml., 5 mg.) q.i.d. Maintenance dosage may be as low as one fourth of the initial dosage. Make downward dosage adjustment as soon as initial symptoms are controlled.

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Opinion & Dialogue

Should a specially prepared package insert be made available to patients?



Dr. Alexander M. Schmidt
Commissioner,
Food and Drug
Administration



Dr. James H. Sammons
Executive Vice President
of the American
Medical Association

The idea of a so-called patient package insert has been around for a long time. Many physicians already use written instruction sheets to provide patients with information about the drugs they are taking. And some physicians give verbal instructions; but in too many instances these are what I call eye-glazing exercises. I have seen patients sit with glazed eyes listening to a rapid-fire lecture by a hurried physician who has 20 people out in his waiting room. These patients aren't given sufficient understanding and therefore do not follow instructions. So I think the idea of an official package insert for patients is a good one. Perhaps we should really think of this kind of information simply as an extension of drug labeling.

The benefits of patient involvement

Many physicians may not realize how frequently a patient obtains his drug information from Aunt Tillie or the next door neighbor. And this information is almost always bad or irrelevant to the case at hand. Furthermore, the incentive to go along with a prescribed program is slim if the only reading matter the patient receives, along with his prescription, is a bill.

As an educator I am impressed by the principle that the best way to get someone to do something is to involve him in the process. So the

I think there are advantages as well as some real disadvantages in a patient package insert. When you begin to use semi-medical or medical terms to describe complications or possible sequelae of disease or treatment, you may frighten the patient—particularly since the more highly sophisticated patient is not the one who is going to read the insert. The patient who will read it is the one most susceptible to fright and confusion by the language.

On the positive side, a package insert will probably give the patient better insight into why he is being treated the way he is, and it may give the physician a little bit more time. But it does not remove from the physician the need or obligation to explain the insert.

Some pitfalls in the inclusion of side effects

Certainly a patient should be warned of the possibility of serious side reactions—to know what the real dangers are. But it doesn't do a bit of good to indicate that a patient on oral penicillin may develop a rash, itching, or a drop in blood pressure. Or that he may faint. I think the real danger is that fright engendered by the insert may possibly outweigh the potential good.

main purpose of drug information for the patient is to get his cooperation in following a drug regimen.

Preparation and distribution of patient drug information

We would hope to amass information from physicians, medical societies, the pharmaceutical industry and centers of medical learning. The ultimate responsibility for uniform labeling must, however, rest with the Food and Drug Administration. There is nothing wrong with this agency saying, "this information is generally agreed upon and therefore it should be used," as long as our process for getting the information is sound.

Distribution of the information is a problem. In great measure it would depend on the medication in question. For example, in the case of an injectable long-acting progesterone, we would think it mandatory to issue two separate leaflets—a short one for the patient to read before getting the first shot and a long one to take home in order to make a decision about continuing therapy. In this case, the information might be put directly on the package and not removable at all. But for a medication like an antihistamine this information might be issued separately, thus giving the physician the option of distribution. This could preserve the placebo use, etc.

It is in the distribution of patient information that the pharmacist may get involved. As professionals and members of the health-care team and as a most important source of drug information to patients, pharmacists should be responsible for keeping medical and drug records on patients. It is also logical that they should distribute drug information to them.

Realistic problems must be considered

We have to expect that the introduction of an information device will also create new problems. First, how can we communicate complex and sophisticated information to people of widely divergent socioeconomic and ethnic groups? Second, what will we say? And third, how can we counteract the negative attitude of many physicians toward any outside influence or input? Hopefully the medical profession will respond by anticipating the problems and helping to solve them. Assuming we can also solve the difficulty of communicating information to diverse groups throughout the United States, our remaining task will be the inclusion of appropriate material.

What information is appropriate?

In my opinion, technical, chemical and such types of material should not be included. And there is no point in the routine listing of side effects like nausea and vomiting which seem to apply to practically all drugs, unless it is common with the drug. However, serious side effects should be listed, as should information about a medication that is potentially risky for other reasons.

Other pertinent information might consist of drug interactions, the need for laboratory follow-up, and special storage requirements. What we want to include is information that will help increase patient compliance with the therapy.

Positive aspects of patient drug information

Labeling medication for the patient would accomplish a number of good things: the patient could be on the lookout for possible serious side effects; his compliance would increase through greater understanding; the physician would be a better source of information since he would be freer to use his time more effectively; other members of the health-care team would benefit through patient understanding and cooperation; and, finally, the physician-patient relationship would probably be enhanced by the greater understanding on the part of the patient of what the physician is doing for him.

Only the doctor can remove that fear by 20 or 30 minutes of conversation.

I'm not suggesting that we withhold any information from the patient because, first of all, it would be totally dishonest and secondly, it would defeat the very purpose of the insert. I do think that a patient on the birth control pill should know about the incidence of phlebothrombosis.

If you're going to tell a patient the incidence of serious adverse reactions, then you have to tell him that a concerned medical decision was made to use a particular medication in his situation after careful consideration of the incidence of complications or side effects.

Emotionally unstable patients pose a special problem

There are patients who, because of severe emotional problems, could not handle the information contained in a patient package insert. Yet if we are going to have a package insert at all, we just can't have two inserts. I think we might simply have to tell the families of these patients to remove the insert from the package.

Legal implications of the patient package insert

Just what effect would a patient package insert have on malpractice? We could try to avoid any legal implications by pointing out that the physician has selected a particular medication because, in his professional judgment, it is the treatment of choice. For instance, you can't tell everyone taking antihistamines not to work just because a few patients develop extreme drowsiness which can lead to accidents. And what about the very small incidence of aplastic anemia rarely associated with chloramphenicol? If, based on sensitivity studies and other criteria, we decide to employ this particular antibiotic, we do so in full knowledge of this serious potential side effect. It's not a simple problem.

How do we handle an insert for medication used for a placebo effect?

With rare exceptions, physicians no longer use medications for a placebo effect. This question does raise the issue of how a patient may react to receiving a medication without a package insert.

Preparation of the package insert

The development of the insert ought to be a joint operation between physicians, the pharmaceutical industry, the A.M.A. and the F.D.A.

I view the A.M.A.'s role as a coordinator or catalyst. It is the only organization through which the profession as a whole, irrespective of specialty, can speak. It has relatively instant access to all the medical expertise in this country. And it can bring that professional expertise together to ensure a better package insert. The A.M.A. can work in conjunction with the industry that has produced the product and which is ultimately going to supply the insert.

I don't think we should rely, or expect to rely, on legislative committees and their nonprofessional staffs to make these decisions when it is perfectly within the power of the two groups to resolve the issues in the very best American tradition—without the government forcing us to do it. I think the F.D.A. has to be involved, but I'd like them to become involved because they were asked to become involved.

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Meclizine HCl is contraindicated in individuals who have shown a previous hypersensitivity to it.

WARNINGS. Since drowsiness may, on occasion, occur with use of this drug, patients should be warned of this possibility and cautioned against driving a car or operating dangerous machinery.

Usage in Children: Clinical studies establishing safety and effectiveness in children have not been done; therefore, usage is not recommended in the pediatric age group.

Usage in Pregnancy: See "Contraindications."

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Editorials

Intracranial Ependymomas

DR. VINCENT'S* CASE report of a posterior fossa ependymoma in a 62-year-old man illustrates well the capability of this tumor to extend through the lateral recess into the cerebellopontine angle (CPA). Parenthetically it should be recalled that this tumor can also arise primarily from the lateral medullary velum to grow in the CPA.[1] Unfortunately, in the case reported the main midline mass of the tumor was not recognized in the contrast studies or at surgery and the tissue misdiagnosed resulting in suboptimal treatment.

The statement that pantopaque cisternography is the diagnostic procedure of choice for posterior fossa ependymomas is erroneous. Fokes and Earle[2] stated their preference for pantopaque ventriculography although angiography, particularly with the subtraction techniques for posterior fossa study, and air ventriculography are highly reliable studies for recognition of the presence of these tumors. In any patient with suspected intracranial mass lesion, particularly with symptoms of increased intracranial pressure, a diagnostic procedure requiring spinal puncture such as pantopaque cisternography (or fractional pneumoencephalogram) carries increased risk and if to be done should only be performed when prepared to proceed directly with definitive surgery.

As suggested by Dr. Vincent, computerized axial tomography has become the single most helpful test in suspected intracranial tumors, both supra and infratentorial, and carries with it no risk to the patient. Tumor enhancement with an intravenous contrast agent further increases tumor definition.

Spinal subarachnoid seeding of ependymomas, found in one-third of the cases of Tarlov and Davidoff[3] and in one-half of those cases with fourth ventricular ependymomas studies by Svein et al.[4] can hardly be called rare. More likely, as found in the analysis by Svein, they may be present but asymptomatic. Conversely we have seen patients present with symptoms and signs due to cauda equina ependymoma secondarily found to be arising from an intracranial source. Such findings raise the question of the advisability of including the spinal axis in the field of radiation treatment in every patient with a fourth ventricular ependymoma. At present the morbidity of this treatment inclines most therapists to withhold radiation of the spinal axis until symptoms or signs of seeding are manifest.[5]

Undoubtedly the past decade has brought about a significant improvement in the stated ependymoma operative mortality rate of 20 percent. Hopefully more effective therapeutic measures used as adjuncts to surgery, particularly chemotherapeutic agents, will be forthcoming to significantly improve long-term survival statistics.

David G. Piepgras, M.D.
Rochester, Minnesota

*See page 877.

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Mental Health Planning in a Children's Hospital

HOSPITALS WERE ESTABLISHED to meet the needs and convenience of the doctor, with a concentration of resources to aid the delivery of his skills and services. Patient needs and any inconveniences caused by hospitalization were tolerated and given a low priority with the expanding medical technology. The hospitals themselves have become more imposing monuments to this technology and it would appear that the hospital itself has begun to shape the practice of medicine.

With children, we extrapolated the methods of working with adults and our primary focus was to create procedures which created the smallest amount of inconvenience to us. Parents were invariably viewed as a problem, as children were usually more cooperative in their parents' absence. The quiet, compliant, occasionally depressed child was described as a good patient. We have not been required to look at the costs of such management.

A short time ago, Renee Spitz[1] discovered that a medical condition, marasmus or failure to thrive, responded to a missing ingredient, touching and handling by mother or mother substitutes. His discoveries have led to an entire philosophy of child management. For a time we believed that regression, when children showed signs of a withdrawal to a more immature pattern of behavior was a necessary or frequently observed result of hospitalization and surgical procedures. It became accepted. Only when we began to consider the number of children who did not regress under the stress of hospitalization[2] did we note that with the right circumstances, some children went through the procedures with surprising ease, with an enhanced feeling of self-esteem, of accomplishment.[3] Possibly hospitalization could be normalized or detraumatized with some careful planning and effort.

With this in mind, a very devoted group has spent much time and effort in designing a hospital and hospital experience with an effort to put the needs of children first and shape the medical process around them. The result of these efforts is present in our community as Children's Health Center. Not ideas, but approaches, programs and results. Starting with the architecture, but continuing into the style of medical practice, the hospital has been shaped around the healthy growth potential of childhood. A tour of this facility reveals such thought.

Parents and siblings are not ignored or set aside, but are included in the experience. From the rocking chairs in the intensive-care nursery to the rooming-in facilities for parents to a unit designed for easy intrusion by children, primary growth needs have come first. Instead of making medical practice more cumbersome and difficult, in some areas as anesthesia induction, the contributions of the mental health team have resulted in easier and safer medical practice.

The most unique and laudable feature of this hospital is the role of the mental health ecologist. This position is not an ancillary, "added on" or paramedical function. It is built right into the hospital by nature of its definition on a vice-presidential level in the hospital superstructure. The ecologist, then, is in a position to define and implement programs and attitudes, not merely to advise from the sidelines. Without this careful thought (and clout) mental health ecology would still be a quaint idea. We learn some lessons slowly, occasionally we need to be convinced.

Though Dr. Wallinga's article* describes the hospital in detail, an article alone cannot do justice to this pioneering institution. We owe a debt of gratitude to the selfless individuals who dreamed, designed, built and operate such a sensitive and vital facility.

Ronald Kyllonen, M.D.
Minneapolis, Minnesota

*See page 911.

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patients may need...

- Diet control
- A proven cholesterol-lowering adjunct to diet*
- Convenient once-a-day dosage*
- Reasonable cost*



*Choloxin®
(sodium dextrothyroxine)

An agent for low density lipoproteins, "type II hy[illegible]id," in euthyroid, non-cardiac patients.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES, INC.
Deerfield, Illinois 60015

Choloxin® (sodium dextrothyroxine)

The Lipid-Lowering Agent with Once-A-Day Dosage

Four strengths . . . 1, 2, 4, and 6 mg. . . . are available making the scored tablet regimen a flexible dosage system. And, for most patients, CHOLOXIN tablets offer once-a-day dosage.

AN IMPORTANT NOTE:
It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

CHOLOXIN® (sodium dextrothyroxine) Single-Tablet-A-Day Dosage Schedules

See prescribing information in package insert reproduced below.

	Starting Dosage	Increased Monthly by	Usual Maintenance	Maximal Recommended
Adult Hypercholesterolemic	1.0-2.0 mg.	1.0-2.0 mg.	4.0-8.0 mg.	4.0-8.0 mg.
Pediatric Hypercholesterolemic	0.05 mg./kg. body weight	0.05 mg./kg.	0.1 mg./kg. body weight	4.0 mg.
Hypothyroid Cardiac	0.5-1.0 mg.	1.0 mg.	4.0 mg.	4.0 mg.

Choloxin®
(sodium dextrothyroxine)

Description
CHOLOXIN (sodium dextrothyroxine) is the sodium salt of the dextrorotatory isomer of thyroxine. It is chemically described as D-3,5,3′,5′-tetraiodothyronine sodium salt.

Actions
The predominant effect of CHOLOXIN (sodium dextrothyroxine) is the reduction of serum cholesterol levels in hyperlipidemic patients. Beta lipoprotein and triglyceride fractions may also be reduced from previously elevated levels.

Most of the available evidence indicates that CHOLOXIN stimulates the liver to increase catabolism and excretion of cholesterol and its degradation products via the biliary route into the feces. Cholesterol synthesis is not inhibited and abnormal metabolic end-products do not accumulate in the blood.

Indications
This is not an innocuous drug. Strict attention should be paid to the indications and contraindications.

CHOLOXIN (sodium dextrothyroxine) is an antilipidemic agent used as an adjunct to diet and other measures for the reduction of elevated serum cholesterol (low density lipoproteins) in euthyroid patients with no known evidence of organic heart disease.

The drug is also indicated in the treatment of hypothyroidism in patients with cardiac disease who cannot tolerate other types of thyroid medication.

Before prescribing, note the following: Results from a randomized clinical study have indicated a possible adverse effect when CHOLOXIN is administered to a patient receiving a digitalis preparation. There may be an additive effect. This additive effect may possibly stimulate the myocardium excessively in patients with significant myocardial impairment. CHOLOXIN dosage should not exceed 4 mg per day when the patient is receiving a digitalis preparation concomitantly. Careful monitoring of the total effect of both drugs is important.

It has not been established whether the drug-induced lowering of serum cholesterol or lipid levels has a detrimental, beneficial, or no effect on the morbidity or mortality due to atherosclerosis or coronary heart disease. Several years will be required before current investigations will yield an answer to this question.

Contraindications
The administration of CHOLOXIN (sodium dextrothyroxine) to euthyroid patients with one or more of the following conditions is contraindicated:

1. Known organic heart disease, including angina pectoris; history of myocardial infarction; cardiac arrhythmia or tachycardia, either active or in patients with demonstrated propensity for arrhythmias; rheumatic heart disease; history of congestive heart failure; and decompensated or borderline compensated cardiac status.
2. Hypertensive states (other than mild, labile systolic hypertension).
3. Advanced liver or kidney disease.
4. Pregnancy.
5. Nursing mothers.
6. History of iodism.

Warnings
CHOLOXIN (sodium dextrothyroxine) may potentiate the effects of anticoagulants on prothrombin time. Reductions of anticoagulant dosage by as much as 30% have been required in some patients. Consequently, the dosage of anticoagulants should be reduced by one-third upon initiation of CHOLOXIN therapy and the dosage subsequently readjusted on the basis of prothrombin time. The prothrombin time of patients receiving anticoagulant therapy concomitantly with CHOLOXIN therapy should be observed as frequently as necessary, but at least weekly, during the first few weeks of treatment.

In the surgical patient, it is wise to consider withdrawal of the drug two weeks prior to surgery if the use of anticoagulants during surgery is contemplated.

When CHOLOXIN is used as thyroid replacement therapy in hypothyroid patients with concomitant coronary artery disease (especially those with a history of angina pectoris or myocardial infarction) or other cardiac disease, treatment should be initiated with care. Special consideration of the dosage schedule of CHOLOXIN is required. This drug may increase the oxygen requirements of the myocardium, especially at high dosage levels. Treated subjects with coronary artery disease must be seen at frequent intervals. If aggravation of angina or increased myocardial ischemia, cardiac failure, or clinically significant arrhythmia develops during the treatment of hypothyroid patients, the dosage should be reduced or the drug discontinued.

Special consideration must be given to the dosage of other thyroid medications used concomitantly with CHOLOXIN. As with all thyroactive drugs, hypothyroid patients are more sensitive to a given dose of CHOLOXIN than euthyroid patients.

Epinephrine injection in patients with coronary artery disease may precipitate an episode of coronary insufficiency. This condition may be enhanced in patients receiving thyroid analogues. These phenomena should be kept in mind when catecholamine injections are required in sodium dextrothyroxine-treated patients with coronary artery disease.

Since the possibility of precipitating cardiac arrhythmias during surgery may be greater in patients treated with thyroid hormones, it may be wise to discontinue CHOLOXIN in euthyroid patients at least two weeks prior to an elective operation. During emergency surgery in euthyroid patients, and in surgery in hypothyroid patients in whom it may be advisable to withdraw therapy, the patients should be carefully observed.

There are reports that sodium dextrothyroxine in diabetic patients is capable of increasing blood sugar levels with a resultant increase in requirements of insulin or oral hypoglycemic agents. Special attention should be paid to parameters necessary for good control of the diabetic state in dextrothyroxine-treated subjects and to dosage requirements of insulin or other antidiabetic drugs. If sodium dextrothyroxine is later withdrawn from patients who had required an increase of insulin (or oral hypoglycemic agents) dosage during its administration, the dosage of antidiabetic drugs should be reduced and adjusted to maintain good control of the diabetic state.

When either or both impaired liver or kidney function are present, the advantages of CHOLOXIN therapy must be weighed against the possibility of deleterious results.

Usage in Women of Childbearing Age
Women of childbearing age with familial hypercholesterolemia or hyperlipemia should not be deprived of the use of this drug; it can be given to those patients exercising strict birth control procedures. Since pregnancy may occur despite the use of birth control procedures, administration of CHOLOXIN (sodium dextrothyroxine) to women of this age group should be undertaken only after weighing the possible risk to the fetus against the possible benefits to the mother. Teratogenic studies in two animal species have resulted in no abnormalities in the offspring.

Precautions
It is expected that patients on dextrothyroxine therapy will show greatly increased serum protein-bound-iodine levels. These increased serum PBI values are evidence of absorption and transport of the drug, and should NOT be interpreted as evidence of hypermetabolism; similarly, they may not be used for titrating the effective dose of CHOLOXIN (sodium dextrothyroxine). PBI values in the range of 10 to 25 mcg% in treated patients are common.

If signs or symptoms of iodism develop during CHOLOXIN therapy, the drug should be discontinued.

A few children with familial hypercholesterolemia have been treated with CHOLOXIN for periods of one year or longer with no adverse effects on growth. However, it is recommended that the drug be continued in patients in this age group only if a significant serum cholesterol-lowering effect is observed.

Adverse Reactions
The side effects attributed to dextrothyroxine therapy are, for the most part, due to increased metabolism, and may be minimized by following the recommended dosage schedule. Adverse effects are least commonly seen in euthyroid patients with no signs or symptoms of organic heart disease; the incidence of adverse effects is increased in hypothyroid patients, and is highest in those patients with organic heart disease superimposed on the hypothyroid state.

In the absence of known organic heart disease, some cardiac changes may be precipitated during sodium dextrothyroxine therapy. In addition to angina pectoris, arrhythmia consisting of extrasystoles, ectopic beats, or supraventricular tachycardia, ECG evidence of ischemic myocardial changes and increase in heart size have been observed. Myocardial infarctions, both fatal and non-fatal, have occurred, but these are not unexpected in untreated patients in the age groups studied. It is not known whether any of these infarcts were drug related.

Changes in clinical status that may be related to the metabolic action of the drug include the development of insomnia, nervousness, palpitations, tremors, loss of weight, lid lag, sweating, flushing, hyperthermia, hair loss, diuresis, and menstrual irregularities. Gastrointestinal complaints during therapy have included dyspepsia, nausea and vomiting, constipation, diarrhea, and decrease in appetite.

Other side effects reported to be associated with CHOLOXIN (sodium dextrothyroxine) therapy include the development of headache, changes in libido (increase or decrease), hoarseness, tinnitus, dizziness, peripheral edema, malaise, tiredness, visual disturbances, psychic changes, paresthesia, muscle pain, and various bizarre subjective complaints. Skin rashes, including a few which appeared to be due to iodism, and itching have been attributed to dextrothyroxine by some investigators. Gallstones have been discovered in occasional dextrothyroxine-treated patients and cholestatic jaundice has occurred in one patient, although its relationship to CHOLOXIN therapy was not established.

In several instances, the previously existing conditions of the patient appeared to continue or progress during the administration of CHOLOXIN; a worsening of peripheral vascular disease, sensorium, exophthalmos, and retinopathy have been reported.

CHOLOXIN potentiates the effects of anticoagulants, such as warfarin or Dicumarol, on prothrombin time, thus indicating a decrease in the dosage requirements of the anticoagulants. On the other hand, dosage requirements of antidiabetic drugs have been reported to be increased during dextrothyroxine therapy (see WARNINGS section).

Dosage and Administration
For **adult** euthyroid hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN (sodium dextrothyroxine) is 4 to 8 mg per day. The initial daily dose should be 1 to 2 mg to be increased in 1 to 2 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, if that dosage level is indicated to effect the desired lowering of serum cholesterol.

When used as partial or complete substitution therapy for levothyroxine in hypothyroid patients with cardiac disease who cannot tolerate other types of thyroid medication, the initial daily dose should be 1 mg to be increased in 1 mg increments at intervals of not less than one month to a maximum level of 4 to 8 mg daily, preferably the lower dosage. The maximum in patients receiving digitalis therapy is 4 mg.

For **pediatric** hypercholesterolemic patients, the recommended maintenance dose of CHOLOXIN is approximately 0.1 mg per kilogram. The initial daily dosage should be approximately 0.05 mg per kilogram to be increased in up to 0.05 mg per kilogram increments at monthly intervals. The recommended maximal dose is 4 mg daily, if that dosage is indicated to effect the desired lowering of serum cholesterol.

If new signs or symptoms of cardiac disease develop during the treatment period, the drug should be withdrawn.

How Supplied
CHOLOXIN (sodium dextrothyroxine) is supplied in prescription packages of scored 1, 2, 4, and 6 mg tablets.

FLINT LABORATORIES
DIVISION OF TRAVENOL LABORATORIES INC
Deerfield, Illinois 60015

Minnesota Department of Health

Hypertension Control

D. S. Fleming, M.D.*; Sidney Finkelstein, M.D.†; J. G. Papra‡; and G. R. Twogood#

In recent years, there has been an increasing awareness of the effects of untreated hypertension on the mortality and morbidity of the American public. Since treatment before the occurrence of end-organ disease can result in decreased deaths and disability, it would seem that official health agencies have the responsibility for early identification and referral of the hypertensive reservoir in our population. In 1974, the Minnesota Department of Health began screening individuals for hypertension and referring those with elevated blood pressure to physicians for treatment.

A large percentage of hypertensives are not being adequately treated. The formula "½x½x ½" is descriptive of the problem: one-half of those with hypertension do not know that they have this disease; of the half who know that they have hypertension, half are not currently under physicians' care for it; and of those aware of their hypertension and under treatment, half are not under adequate blood pressure control. Therefore, only one-eighth of all hypertensives are adequately controlled. Screening is a useful tool to identify many hypertensive individuals, and refer them to physicians.

The task of identifying individuals who need referral is large. The 1962 National Health Examination Survey[1], which is still the definitive work on hypertension prevalence, found that 23 million adult Americans had a blood pressure equal to, or greater than, 160 mm Hg. systolic and/or 95 mm Hg. diastolic. The prevalence rate for Minnesota was about 10%. This means that we would expect that there are more than 200,000 adult Minnesota residents with hypertension. They are distributed among more than 2,000,000 adult residents of the state.

The Minnesota Department of Health is directing hypertension screening principally at working-age adults. These people are being screened in congregate—at work, or at a conference or convention. The Minnesota Department of Health is organizing and coordinating screening, which is actually done by local agencies. The principal participants are Red Cross nursing chapters, county public health services, and school district nursing services.

In 1974, 50,892 adults were screened, of whom 6,638 (about one of eight) had blood pressures at the screening site of over 160 systolic and/or 95 diastolic. Detailed analysis of the first 24,000

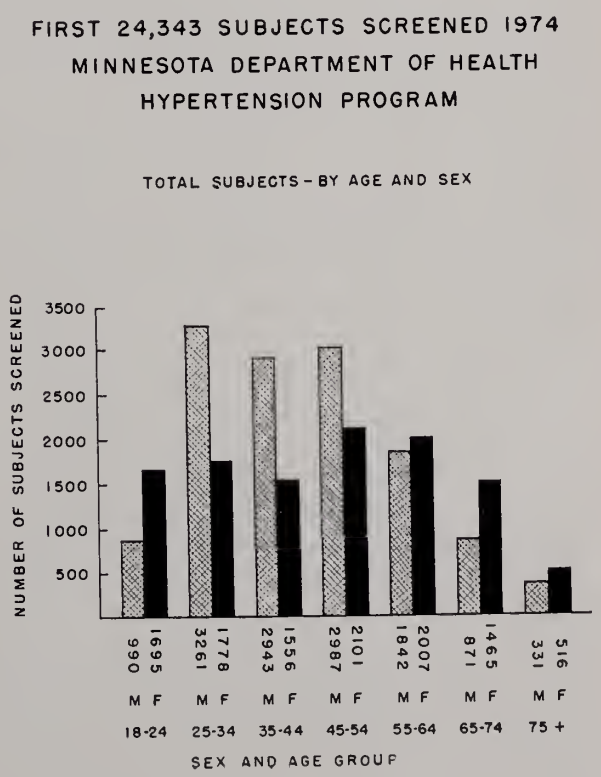


Figure 1

*Former Division Director, Personal Health Services, Minnesota Department of Health, Minneapolis.
†Chief, Adult Health Section, Minnesota Department of Health, Minneapolis.
‡Coordinator, Hypertension Control Program, Minnesota Department of Health, Minneapolis.
#Program Representative, Minnesota Department of Health, Minneapolis.

adults screened yielded the information contained in the summary. There was a strong association of overweight with high blood pressure, (see Summary, part B). It is noteworthy that 43% of those people who claimed to be currently on treatment for hypertension had blood pressure over 160/95, indicating inadequate control.

Summary and the Table, with Figures 1 and 2, show that the program has been effective in reaching working-age individuals of both sexes. The screening approach being used avoids, to some degree, the population bias inherent in "Shopping Center" screening, where the screened population is often skewed towards females and the elderly. Figure 2 shows the numbers and Figure 3 the percentages of subject by age and sex, with pressures above the screening levels. The findings of pressures above the screening level are reasonably comparable to rates found nationally.

At time of screening, all individuals are informed of their blood pressure levels. If the pressure is above 140/90, the individual is told that he or she has an elevated reading and it is suggested that he or she have a retest by a physician. If the pressure is above 160/95, the individual is advised to see a physician for a retest, that we will notify the physician by mail of the screening blood pressure, and that we will contact the individual by mail to learn of the physician's evaluation for purposes of program evaluation.

All 6,638 persons with blood pressures over 160/95 received, at most, two letters from the Department to obtain follow-up information. The results of these replies are described in the Table. Approximately 60% of those who indicated that they did visit their physicians received confirmation of having hypertension. The rate is comparable to that observed in other screening programs.

To date, program activity has been centered on the identification and referral of hypertensives. The issues of patient retention and patient education are now under consideration in order that we may develop services which will help the newly identified patient become a responsible and cooperative partner in his or her successful long-term treatment. Valuable advice on these and other aspects of hypertension control has been provided by the Technical Advisory Committee on Hypertension (see list published at the end of this article).

The data presented represents the first year's work on hypertension control by the Minnesota

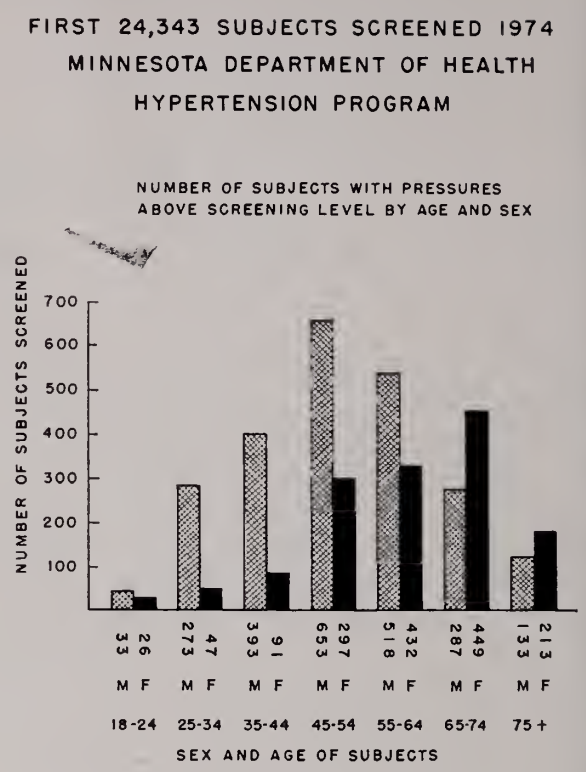


Figure 2

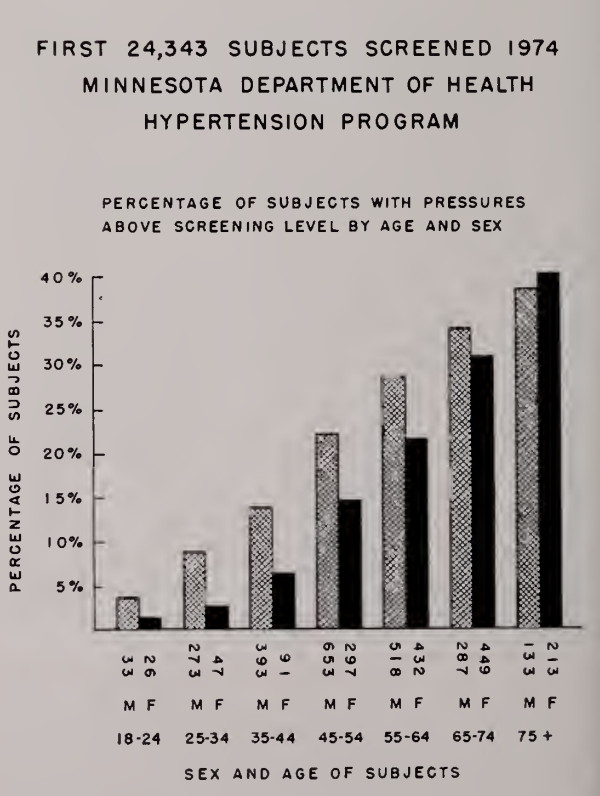


Figure 3

Department of Health. Recommendations by the Department of Health, Education and Welfare stress the necessity that such a program must last at least 10 years to deal effectively with the aforementioned problems of hypertension. The results presented here, therefore, represent only a fraction of the total effort required to deal with hypertension in Minnesota.

Department staff members are encouraging local communities, medical societies, county nursing services, and health agencies to initiate control programs for their communities. Requests for control program assistance can be made to: Minnesota Department of Health, Hypertension Control Program, 717 Delaware Street, S.E., Minneapolis, Minnesota 55440.

TABLE

Response to Follow-up Letters by Individuals Found with Elevated Blood Pressures, 1974

Total individuals with elevated blood pressures followed up by the State Health Department	6,638
Total number of responses	4,313
Total percent of responses	65%
Of the Returns:	
2,663 stated that they subsequently had a physician evaluation with a diagnosis of hypertension	62%
1,650 stated that they subsequently had a physician evaluation and were not, at that time, diagnosed as hypertensive	38%

Summary

Minnesota Department of Health
Blood Pressure Screening
(First 24,000 Adults Screened)

A. Blood Pressure Elevation Related to Sex

	# Persons Surveyed	# with Elevated Blood Pressure*	% with Elevated Blood Pressure
Male	13,225	2,296	17%
Female	11,118	1,555	14%
Total	24,343	3,851	16%

B. Blood Pressure Elevations Related to Weight†

Total Persons of Normal Weight or Underweight	18,102	
Numbers and Percent with Elevated Blood Pressure	2,268	13%
Total Overweight	5,618	
Numbers and Percent with Elevated Blood Pressure	1,465	26%

C. Individuals Claiming Prior Knowledge and/or Treatment for Hypertension

Subjects claimed to be previously diagnosed as hypertensive	4,807	
Total of Survey		20%
Subjects claimed to be on therapy for hypertension	2,105	
Total of Survey		9%

D. Of those subjects claiming to be on therapy for hypertension:

Blood Pressure Under Screening Level*	1,191	57%
Blood Pressure Above Screening Level*	914	43%

*Elevated Blood Pressure means equal to or greater than 160 mm Hg. Systolic and/or 95 mm Hg. Diastolic.

†Calculated through "Mass Body Index"=Weight (K)/Height^2 (Information supplied by subjects): references: J. Chron. Dis. 25:329-343, 1972 and Ann. Int. Med. 77:17, July 1972.

TECHNICAL ADVISORY COMMITTEE ON HYPERTENSION, MINNESOTA DEPARTMENT OF HEALTH

Minnesota Academy of Family Physicians:
Bruce Cameron, M.D.
Matthew Yelle, M.D.
Reino Puumala, M.D.

St. Louis Park Medical Center:
Don Etzwiler, M.D.
Ellen O'Connor

Laboratory of Physiological Hygiene:

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Kidney Foundation of the Upper Mid-West:

Cameron Strong, M.D.
Bruce Briggs
John Dilley
Gaylord Bridge

University of Minnesota School of Medicine:

Louis Tobian, M.D.

References

1. Vital and Health Statistics, Data from the National Health Survey, Hypertension and Hypertensive Heart Disease in Adults, United States-1960-1962, U.S. Department of Health, Education, and Welfare, Public Health Service, May 1966.

Minnesota Academy of Occupational Medicine and Surgery

The Minnesota Academy of Occupational Medicine and Surgery, the local chapter of The American Occupational Medical Association (formerly the IMA) is a professional organization for all physicians concerned with the relationship between health and work and the work environment. Its purposes are to further the education and to advance the knowledge and skills of its members. It also promotes interest, stimulates research, encourages education, and disseminates information directed toward improvement and conservation of the health of employees. The Association seeks to unitc into an active and dynamic organization all physicians fully or partially engaged in the practice of occupational medicine and surgery. Membership offers a monthly journal and a monthly newsletter advising of current activities and regulations affecting occupational medicine and employee health. It was founded in 1953 and meets four times a year, usually on the third Thursday of September, November, February and May. Interested physicians are encouraged to contact Doctor James L. Craig, Secretary, 9200 Wayzata Blvd., Minneapolis, Minnesota 55426, (612) 540-2244.

CME '76

May 20-21, 1976

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MAKES SENSE

TRIAMTERENE CONSERVES POTASSIUM WHILE HYDROCHLOROTHIAZIDE LOWERS BLOOD PRESSURE

FOR LONG-TERM CONTROL OF HYPERTENSION*

Serum K^+ and BUN should be checked periodically. (See Warnings Section.)



Before prescribing, see complete prescribing information in SK&F literature or *PDR*. The following is a brief summary.

* **Warning**
This fixed combination drug is not indicated for initial therapy of edema or hypertension. Edema or hypertension requires therapy titrated to the individual patient. If the fixed combination represents the dosage so determined, its use may be more convenient in patient management. The treatment of hypertension and edema is not static, but must be reevaluated as conditions in each patient warrant.

***Indications:** *Edema:* That associated with congestive heart failure, cirrhosis of the liver, the nephrotic syndrome; steroid-induced and idiopathic edema; edema resistant to other diuretic therapy. *Mild to moderate hypertension:* Usefulness of the triamterene component is limited to its potassium-sparing effect.

Contraindications: Pre-existing elevated serum potassium. Hypersensitivity to either component. Continued use in progressive renal or hepatic dysfunction or developing hyperkalemia.

Warnings: **Do not use dietary potassium supplements or potassium salts unless hypokalemia develops or dietary potassium intake is markedly impaired.** Enteric-coated potassium salts may cause small bowel stenosis with or without ulceration. Hyperkalemia (>5.4 mEq/L) has been reported in 4% of patients under 60 years, in 12% of patients over 60 years, and in less than 8% of patients overall. Rarely, cases have been associated with cardiac irregularities. Accordingly, **check serum potassium during therapy, particularly in patients with suspected or confirmed renal insufficiency (e.g., elderly or diabetics). If hyperkalemia develops, substitute a thiazide alone. If spironolactone is used concomitantly with 'Dyazide', check serum potassium frequently**—both can cause potassium retention and sometimes hyperkalemia. Two deaths have been reported in patients on such combined therapy (in one, recommended dosage was exceeded; in the other, serum electrolytes were not properly monitored). Observe patients on 'Dyazide' regularly for possible blood dyscrasias, liver damage or other idiosyncratic reactions. Blood dyscrasias have been reported in patients receiving Dyrenium (triamterene, SK&F). Rarely, leukopenia, thrombocytopenia, agranulocytosis, and aplastic anemia have been reported with the thiazides. Watch for signs of impending coma in acutely ill cirrhotics. Thiazides are reported to cross the placental barrier and appear in breast milk. This may result in fetal or neonatal hyperbilirubinemia, thrombocytopenia, altered carbohydrate metabolism and possibly other adverse reactions that have occurred in the adult. When used during pregnancy or in women who might bear children, weigh potential benefits against possible hazards to fetus.

Precautions: Do periodic serum electrolyte and BUN determinations. Do periodic hematologic studies in cirrhotics with splenomegaly. Antihypertensive effects may be enhanced in postsympathectomy patients. The following may occur: hyperuricemia and gout, reversible nitrogen retention, decreasing alkali reserve with possible metabolic acidosis, hyperglycemia and glycosuria (diabetic insulin requirements may be altered), digitalis intoxication (in hypokalemia). Use cautiously in surgical patients. Concomitant use with antihypertensive agents may result in an additive hypotensive effect. 'Dyazide' interferes with fluorescent measurement of quinidine.

Adverse Reactions: Muscle cramps, weakness, dizziness, headache, dry mouth; anaphylaxis; rash, urticaria, photosensitivity, purpura, other dermatological conditions; nausea and vomiting (may indicate electrolyte imbalance), diarrhea, constipation, other gastrointestinal disturbances. Necrotizing vasculitis, paresthesias, icterus, pancreatitis, xanthopsia and, rarely, allergic pneumonitis have occurred with thiazides alone.

Supplied: Bottles of 100 capsules; in Single Unit Packages of 100 (intended for institutional use only).

SK&F Co., Carolina, P.R. 00630
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the "empty nest syndrome"

TRIAVIL®

containing perphenazine and amitriptyline HCl
a tranquilizer-antidepressant

for depression with moderate anxiety

in many cases a result of the "empty nest syndrome"

The mid-life crisis: a critical crossroad

Preparation for change—intellectually, vocationally (or avocationally), and emotionally—can often help the menopausal-aged woman cope successfully with a new and different role after the children are grown and gone. Even when these changes have been anticipated and prepared for, a mid-life depression with moderate anxiety is not uncommon—a syndrome often uncontrolled by counseling or other appropriate measures and for which specific medication may be required.

When depression with moderate anxiety persists, TRIAVIL can often help

TRIAVIL provides a highly effective antidepressant and tranquilizer for symptomatic relief of *both* depression and coexisting moderate anxiety. The patient may be able to function more effectively in her daily life.

Many symptoms associated with depression and anxiety such as insomnia, fatigue, anorexia, and functional G.I. complaints, are frequently alleviated. More complete symptomatic relief is usually afforded than with an antidepressant or a tranquilizer alone. In fact, when anxiety masks the depressive state, treatment with just a tranquilizer may deepen the depression and delay symptomatic improvement.

Advantages of the two components in TRIAVIL taken together

A single tablet containing both an antidepressant and a tranquilizer encourages patients to take medication properly and reduces the risk of dosage confusion and error. Cost of therapy to the patient is usually less. To date, clinical evaluations have revealed no undesirable reactions peculiar to the combination. Tablets TRIAVIL are available in four different combinations affording flexibility and individualized dosage adjustment.

Treatment with TRIAVIL—a balanced view

Contraindicated in CNS depression from drugs; in the presence of evidence of bone marrow depression; and in patients hypersensitive to phenothiazines or amitriptyline. Should not be used during the acute recovery phase following myocardial infarction or in patients who have received an MAOI within two weeks. Patients with cardiovascular disorders should be watched closely. Not recommended in children or during pregnancy. The drug may impair mental or physical abilities required in the performance of hazardous tasks and may enhance the response to alcohol. Antiemetic effect may obscure toxicity due to other drugs or mask other disorders. Since suicide is a possibility in any depressive illness, patients should not have access to large quantities of the drug. Hospitalize as soon as possible any patient suspected of having taken an overdose.

For additional prescribing information, please turn to the following page.

MSD
MERCK SHARP & DOHME

for highly effective relief of depression with moderate anxiety

TRIAVIL®

containing perphenazine and amitriptyline HCl a tranquilizer-antidepressant

Available:

TRIAVIL® 2-25: Each tablet contains 2 mg perphenazine and 25 mg amitriptyline HCl

TRIAVIL® 2-10: Each tablet contains 2 mg perphenazine and 10 mg amitriptyline HCl

TRIAVIL® 4-25: Each tablet contains 4 mg perphenazine and 25 mg amitriptyline HCl

TRIAVIL® 4-10: Each tablet contains 4 mg perphenazine and 10 mg amitriptyline HCl

INITIAL THERAPY FOR MANY PATIENTS
TRIAVIL® 2-25 (or TRIAVIL® 4-25) t.i.d. or q.i.d.

FOR FLEXIBILITY IN ADJUSTING MAINTENANCE THERAPY
TRIAVIL® 2-10 (or TRIAVIL® 4-10)

CONTRAINDICATIONS: Central nervous system depression from drugs (barbiturates, alcohol, narcotics, analgesics, antihistamines); bone marrow depression; known hypersensitivity to phenothiazines or amitriptyline. Do not give concomitantly with MAOI drugs because hyperpyretic crises, severe convulsions, and deaths have occurred from such combinations. Allow minimum of 14 days between therapies, then initiate therapy with TRIAVIL cautiously, with gradual increase in dosage until optimum response is achieved. Not recommended for use during acute recovery phase following myocardial infarction.

WARNINGS: TRIAVIL should not be given with guanethidine or similarly acting compounds. Use cautiously in patients with history of urinary retention, angle-closure glaucoma, increased intraocular pressure, or convulsive disorders. In patients with angle-closure glaucoma, even average doses may precipitate an attack. Patients with cardiovascular disorders should be watched closely. Tricyclic antidepressants, including amitriptyline HCl, particularly in high doses, have been reported to produce arrhythmias, sinus tachycardia, and prolongation of conduction time. Myocardial infarction and stroke have been reported with tricyclic antidepressant drugs. Close supervision is required for hyperthyroid patients or those receiving thyroid medication. Caution patients performing hazardous tasks, such as operating machinery or driving motor vehicles, that drug may impair mental and/or physical abilities. Not recommended in children or during pregnancy.

PRECAUTIONS: Suicide is a possibility in depressed patients and may remain until significant remission occurs. Such patients should not have access to large quantities of this drug.

Perphenazine: Should not be used indiscriminately. Use with caution in patients who have previously exhibited severe adverse reactions to other phenothiazines. Likelihood of untoward actions is greater with high doses. Closely supervise with any dosage. The antiemetic effect of perphenazine may obscure signs of toxicity due to overdosage of other drugs or make more difficult the diagnosis of disorders such as brain tumor or intestinal obstruction. A significant, not otherwise explained, rise in body temperature may suggest individual intolerance to perphenazine, in which case discontinue.

If hypotension develops, epinephrine should not be employed, as its action is blocked and partially reversed by perphenazine. Phenothiazines may potentiate the action of central nervous system depressants (opiates, analgesics, antihistamines, barbiturates, alcohol) and atropine. In concurrent therapy with any of these, TRIAVIL should be given in reduced dosage. May also potentiate the action of heat and phosphorous insecticides.

Amitriptyline: In manic-depressive psychosis, depressed patients may experience a shift toward the manic phase if they are treated with an antidepressant. Patients with paranoid symptomatology may have an exaggeration of such symptoms. The tranquilizing effect of TRIAVIL seems to reduce the likelihood of this effect. When amitriptyline HCl is given with anticholinergic agents or sympathomimetic drugs, including epinephrine combined with local anesthetics, close supervision and careful adjustment of dosages are required.

Caution is advised if patients receive large doses of ethchlorvynol concurrently. Transient delirium has been reported in patients who were treated with 1 g of ethchlorvynol and 75-150 mg of amitriptyline HCl.

Amitriptyline HCl may enhance the response to alcohol and the effects of barbiturates and other CNS depressants.

Concurrent administration of amitriptyline HCl and electroshock therapy may increase the hazards associated with such therapy. Such treatment should be limited to patients for whom it is essential. Discontinue several days before elective surgery if possible. Elevation and lowering of blood sugar levels have both been reported.

ADVERSE REACTIONS: Similar to those reported with either constituent alone.

Perphenazine: Side effects may be any of those reported with phenothiazine drugs: extrapyramidal symptoms (opisthotonus, oculogyric crisis, hyperreflexia, dystonia, akathisia, acute dyskinesia, ataxia, parkinsonism) can usually be controlled by the concomitant use of effective antiparkinsonian drugs and/or by reduction in dosage, but sometimes persist after discontinuation of the phenothiazine.

Tardive dyskinesia may appear in some patients on long-term therapy or may occur after drug therapy with phenothiazines and related agents has been discontinued. The risk appears to be greater in elderly patients on high-dose therapy, especially females. Symptoms are persistent and in some patients appear to be irreversible. The syndrome is characterized by rhythmical involuntary movements of the tongue, face, mouth, or jaw (e.g., protrusion of tongue, puffing of cheeks, puckering of mouth, chewing movements). Involuntary movements of the extremities sometimes occur. There is no known treatment for tardive dyskinesia; antiparkinsonism agents usually do not alleviate the symptoms. It is advised that all antipsychotic agents be discontinued if the above symptoms appear. If treatment is reinstituted, or dosage of the particular drug increased, or another drug substituted, the syndrome may be masked. It has been suggested that fine vermicular movements of the tongue may be an early sign of the syndrome, and that the full-blown syndrome may not develop if medication is stopped when lingual vermiculation appears.

Other side effects are skin disorders (photosensitivity, itching, erythema, urticaria, eczema, up to exfoliative dermatitis); other allergic reactions (asthma, laryngeal edema, angioneurotic edema, anaphylactoid reactions); peripheral edema; reversed epinephrine effect; hyperglycemia; endocrine disturbances (lactation, galactorrhea, gynecomastia, disturbances of menstrual cycle); altered cerebrospinal fluid proteins; paradoxical excitement; hypertension, hypotension, tachycardia, and ECG abnormalities (quinidine-like effect); reactivation of psychotic processes; catatonic-like states; autonomic reactions, such as dry mouth or salivation, headache, anorexia, nausea, vomiting, constipation, obstipation, urinary frequency or incontinence, blurred vision, nasal congestion, and a change in pulse rate; hypnotic effects; pigmentary retinopathy; corneal and lenticular pigmentation; occasional lassitude, muscle weakness, mild insomnia. Other adverse reactions reported with various phenothiazine compounds include blood dyscrasias (pancytopenia, thrombocytopenic purpura, leukopenia, agranulocytosis, eosinophilia); liver damage (jaundice, biliary stasis); grand mal convulsions; cerebral edema; polyphagia; photophobia; skin pigmentation; and failure of ejaculation.

Amitriptyline: Note: Listing includes a few reactions not reported for this drug, but which have occurred with other pharmacologically similar tricyclic antidepressant drugs. *Cardiovascular:* Hypotension; hypertension; tachycardia; palpitation; myocardial infarction; arrhythmias; heart block; stroke. *CNS and Neuromuscular:* Confusional states; disturbed concentration; disorientation; delusions; hallucinations; excitement; anxiety; restlessness; insomnia; nightmares; numbness, tingling, and paresthesias of the extremities; peripheral neuropathy; incoordination; ataxia; tremors; seizures; alteration in EEG patterns; extrapyramidal symptoms; tinnitus; syndrome of inappropriate ADH (antidiuretic hormone) secretion. *Anticholinergic:* Dry mouth; blurred vision; disturbance of accommodation; constipation; paralytic ileus; urinary retention; dilatation of urinary tract. *Allergic:* Skin rash; urticaria; photosensitization; edema of face and tongue. *Hematologic:* Bone marrow depression including agranulocytosis; leukopenia; eosinophilia; purpura; thrombocytopenia. *Gastrointestinal:* Nausea; epigastric distress; vomiting; anorexia; stomatitis; peculiar taste; diarrhea; parotid swelling; black tongue. *Endocrine:* Testicular swelling and gynecomastia in the male; breast enlargement and galactorrhea in the female; increased or decreased libido; elevated or lowered blood sugar levels. *Other:* Dizziness; weakness; fatigue; headache; weight gain or loss; increased perspiration; urinary frequency; mydriasis; drowsiness; jaundice; alopecia. *Withdrawal Symptoms:* Abrupt cessation after prolonged administration may produce nausea, headache, and malaise. These are not indicative of addiction.

OVERDOSAGE: All patients suspected of having taken an overdosage should be admitted to a hospital as soon as possible. Treatment is symptomatic and supportive. However, the intravenous administration of 1—3 mg of physostigmine salicylate is reported to reverse the symptoms of tricyclic antidepressant poisoning. Because physostigmine is rapidly metabolized, the dosage of physostigmine should be repeated as required particularly if life-threatening signs such as arrhythmias, convulsions, and deep coma recur or persist after the initial dosage of physostigmine. On this basis, in severe overdosage with perphenazine-amitriptyline combinations, symptomatic treatment of central anticholinergic effects with physostigmine salicylate should be considered.

For more detailed information, consult your MSD Representative or see full Prescribing Information.
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Legislative

MSMA Position Statement on Professional Liability Legislation

Chester A. Anderson, M.D.,
Chairman, MSMA Committee on Public Policy

The November issue of MINNESOTA MEDICINE* contained an article by G. R. Diessner, M.D., MSMA President, which he presented to the Special Senate Subcommittee on Medical Malpractice and the Joint House Subcommittee on Medical Malpractice. Dr. Diessner, in his statement, outlined the general nature and status of the malpractice insurance problem in Minnesota, and how it is affecting the practice of medicine and the cost of delivering medical care in Minnesota.

I will attempt to summarize the Association's position with respect to some of the proposed or possible legislative remedies that have been suggested to check the rapid escalation in the cost of professional liability insurance.

At the outset it should be stated that there are no sure cures or panaceas that can or will be legislated. Many of the following proposals are untried or unproven. It is with this in mind that MSMA has taken a somewhat conservative position with respect to malpractice legislation.

Competency of Witnesses

MSMA has placed a high priority in the field of remedial legislation on the enactment of a bill relating to the competency of physicians who testify in medical malpractice cases. Historically, the rule has been that a physician could not be held responsible in a medical malpractice action unless one of his peers testified in court as to the accepted standard of medical care in the community, the specialty in which the defendant physician practices, and that the defendant's actions did not conform to such standard. In recent years, the Minnesota courts have done away with most of the restrictions contained in the historical rule. Today, in Minnesota, any physician is considered competent to testify in a medical malpractice action, whether or not he is licensed to practice in Minnesota, whether or not he practices in the defendant's specialty, whether or not he has ever treated patients, and whether or not he knows anything about the accepted standards of care in Minnesota, unless the trial judge rules that he is not competent to testify.

The result has been the emergence of the professional medical expert which one commentator has characterized as "often of marginal competence in his chosen field; often a self certified expert in many areas of medicine".

MSMA is urging enactment of legislation which in effect would restrict medical testimony to physicians licensed to practice in Minnesota, or a contiguous state, or at least require that medical witnesses be required to be engaged in clinical practice a majority of the time in the specialty of the defendant. This would preclude testimony from the so-called itinerant medical witness who makes a full-time occupation as witness for the plaintiff.

MSMA is suggesting that a provision in this legislation prohibit the defendant physician from being called to give his expert testimony as to the accepted standard of medical care in the community. In 1970 the Minnesota Supreme Court ruled that a defendant could be cross-examined for such purpose and that on that basis of such cross-examination the defendant would be found by the jury to have engaged in medical malpractice. The result is that in a medical malpractice action the physician can be forced to testify against himself.

The plaintiff's bar has objected to such legislation citing the so-called "conspiracy of silence" as the reason outside medical experts are called

*See page 841.

in to testify. This has not been documented as a problem today, and to the extent that there ever was or is today such a "conspiracy of silence" or reluctance of physicians to testify represents not a sinister attitude on the part of the medical profession but rather a sincere difference of opinion between attorneys and physicians as to what constitutes medical malpractice.

A plaintiff's attorney quite naturally will seek medical testimony which agrees with his point of view that there was a deviation from the accepted standard of care.

The fact that he can not find a physician who agrees with him can not in and itself be termed a "conspiracy of silence". Where clear evidence of negligence is present local expert witnesses can and have been found to testify. However, such cases are generally settled out of court, thus obviating the need for expert medical testimony.

Collateral Source Rule

High on MSMA's priority list for remedial legislation is a bill to eliminate the so-called "Collateral Source Rule". Under this rule, a plaintiff in a personal injury or wrongful death action may recover all his medical, hospital, and rehabilitation expenses even though these have been paid in whole or in part by his employer, his insurance company, or the State or Federal governments under the Medicare of Medicaid programs. In such an action, a plaintiff can collect for his loss of wages even though he has been continued by his employer on a sick leave program with full or partial payment of his salary. Finally, for example, if a woman dies as a result of a course of medical treatment which the court holds to have been negligent, her husband can collect for his loss of so-called "consortium" even though he remarries shortly after his first wife's death. Loss of consortium includes not only the value of his wife's services as a homemaker and child raiser, but also the loss of her companionship. Under existing law, it is not permissible in such an action for the defense to introduce evidence showing the extent to which the plaintiff has already been compensated for his financial loss. The bill would permit such evidence to be introduced and would permit the jury to take such evidence into account when assessing a plaintiff's damages. The bill would achieve exactly what is accomplished by the so-called "coordination of benefits" provision in most existing health and accident insurance policies. It would prevent a plaintiff in an action for personal injury or wrongful death from collecting two or three times the amount of his actual financial loss. Enactment of such a law would probably have the greatest immediate impact on insurance costs of any law changes which have been suggested.

Informed Consent

Also considered important and desirable is a bill dealing with the doctrine of informed consent. This doctrine permits a plaintiff in a medical malpractice action to have set aside by the court any written or oral consent he may have given for the medical treatment he received if appropriate disclosures about the treatment or procedure were not made by the physician. If the consent is set aside, the plaintiff, under current legal rules may collect damages without any proof of negligence on the part of the defendant physician. There have been various proposals to establish some reasonable standards of informed consent. MSMA is proposing a bill providing that the only persons competent to testify as to what disclosure should be made by a physician to a patient when obtaining the patient's consent to a medical procedure are those physicians who meet the standards established in the bill relating to the competency of witnesses.

Arbitration and Screening or Review Panels

Bills have been introduced in the legislature which would require a medical malpractice claim to be submitted to arbitration or review by a screening panel. None of these proposals provide that the decisions of the arbitration boards or screening panels are binding upon the participants. MSMA opposes a requirement that all medical malpractice actions be submitted for review by an arbitration board or a screening panel unless the decisions of the board or panel are binding on all parties unless fraud can be proven. Our opposition is based upon the following facts:

a. There is no evidence to support the theory that if the board or panel decides against the plaintiff the claim will be dropped. In fact, most evidence is to the contrary. Insurance carriers in areas where such arbitration or screening programs have been tried on a voluntary basis have either pulled out or insisted that their insurers voluntarily stop submitting to the arbitration process.

b. If a decision against the plaintiff does not end the matter, the result is that he will have a better chance

to win in a court of law, because he has been fully educated as to the defense.

c. The theory that the costs of both the plaintiff and the defendant will be less in such plans than they would be in a court trial because the operations of an arbitration board or screening panel are quicker and less technical than those in a court of law does not always follow in practice. If following a decision on a claim by such a board or panel the plaintiff is free to go into court and retry the matter, the inevitable result will be that the costs of both sides will be increased where a plaintiff elects to do so.

d. As the effectiveness of such arbitration boards and screening panels is not known, a-wait-and-see posture would seem appropriate for Minnesota until sufficient experience is obtained in states which have enacted similar proposals.

While the MSMA opposes legislation for arbitration or screening of medical malpractice claims if the decisions of the arbitration boards or screening panels are not binding on all parties, it supports fully a program where such decisions are binding. For this reason, MSMA has joined with the Minnesota State Bar Association in setting up the joint program for arbitration of medical malpractice claims in the Metropolitan Area. Under this program which is entirely voluntary, no claim for medical malpractice will be submitted to arbitration unless all parties agree to do so; but if they do so, the decision of the arbitration board is binding on all parties. Hopefully, this program after a few years of experience will demonstrate whether or not arbitration offers a solution to the malpractice problems.

MSMA is not sponsoring a bill calling for compulsory and binding arbitration, because of legal doubts as to the constitutionality of such a bill. MSMA is strongly urging the legislature that no non-binding screening, review, or arbitration panel legislation be enacted at this time so as to allow for an evaluation of the effectiveness of the voluntary arbitration program.

Limitation on Awards

Bills have been introduced into the legislature to establish a $500,000 ceiling on the amount of the award a successful plaintiff may recover. MSMA would not oppose the establishment of such limits. However, we do not in the short run view such legislation as extremely desirable for the following reasons:

a. There has only been one settlement and no court awards of more than $500,000 to date in Minnesota in a case of medical malpractice.

b. There is a question as to the constitutionality of a law imposing a limit on a plaintiff's right to collect. A court has already ruled such a law unconstitutional in Idaho.

c. A limitation on awards, if constitutional, could conceivably result in higher average awards, as plaintiffs may seek higher compensation for damages.

Balancing these negative considerations, a limitation on recovery would assist insurance carriers in better projecting risks and facilitate more accurate underwriting.

Limitation on Provider Liability

A dollar limitation on the liability of each individual provider has been suggested in some legislation introduced to date. Basically the same objections enumerated above with respect to limitation of awards would apply here.

It has been proposed that the legislature limit the total liability of the provider and in addition establish a state administered patient compensation or excess awards fund from which successful claimants could collect the amount of the award which exceeded the provider's liability. The state fund would be financed by a surcharge on basic coverage or a tax on insurance carriers providing such coverage.

With some exceptions, adequate excess coverage is presently available for most Minnesota physicians. Enactment of legislation to require the state to assume the role of an insurer carries with it the possibility of added regulation. MSMA is therefore not convinced that it is necessary for the state to involve itself in the professional liability insurance market at this time.

Risk Coverage for Providers Unable to Obtain Insurance

The state under proposed legislation would underwrite basic malpractice insurance coverage for health care providers who can not otherwise obtain such coverage. There are few, if any, known health care providers who have been unable up to the present time to obtain basic malpractice insurance coverage. MSMA feels such legislation is currently unnecessary.

Ad Damnum Clause

Complaints filed in many medical malpractice claims tend to exceed to a great extent, often 50 to 100 times, the amount of the financial damage the plaintiff expects to prove.

Publicity with respect to the filing of medical malpractice claims involving huge amounts of

damages is embarrassing for the physician involved. It is felt that this type of publicity may encourage the filing of speculative claims by persons impressed by the possibility of securing large awards.

For these reasons MSMA supports and encourages the elimination of the so-called "ad damnum clause" or the amount of damages sought in the complaint either by court rule or by legislation.

Surety Bond for Recovery of Court Costs

MSMA will support legislation to authorize a court to require a plaintiff in a medical malpractice action to post a surety bond to cover the court costs and attorney fees of the defendant. The defendant would then collect his court costs and attorney fees from this bond if the case is dismissed as frivolous. MSMA does not view this as a big priority however.

Statute of Limitations

The present statute of limitations in Minnesota requires suits to be filed within two years of the date of last treatment. MSMA feels the present law adequately protects both the patient and the physician. MSMA will not seek any change in the present law as regards the statute of limitations.

Contingent Fee Regulation

The contingent fee system has in the opinion of many physicians contributed to the escalation of malpractice insurance costs. There are suggestions for legislation which would set limits on contingent fees; however, the constitutionality of such legislation is likely to be challenged. Any limitation or regulation of contingency fees may more appropriately result from court rule changes by the Minnesota Supreme Court as has been done in New Jersey. MSMA will not seek legislative remedies to correct any inequities of the contingency system.

Reporting of Awards to the State Board of Medical Examiners

While the incompetent physician is not the primary cause of most malpractice problems, the repeat offender should be reviewed at some point by his peers as to his competence and continuing fitness to practice. Accordingly, MSMA will sponsor legislation to require reports to the State Board of Medical Examiners on all medical malpractice awards or settlements over some specified amount for review at an appropriate time.

I have in the foregoing discussed only some of the suggested legislative remedies that have been proposed, and MSMA's position with respect thereto. None of these will completely solve the problem of mounting professional liability insurance costs. At best they may be considered only band-aid approaches to a serious hemorrhage.

The legislature can help but in the final analysis the solution must lie with us, the physicians. We must educate ourselves to take a little more time to talk with our patients, to be a little more considerate of their welfare, and to continually bear in mind that a satisfied patient seldom sues.

If we make the concerted effort necessary to do these things we will have started to solve the current and growing crisis in medical malpractice insurance costs.

Chemical Dependency Symposium, Hennepin County Medical Center
December 9, 1975

Dr. Charles E. Becker, Assistant Professor of Medicine, University of California, Medical School, San Francisco, and Director of Acute Detoxification Unit of the San Francisco General Hospital, will be the guest speaker at a Chemical Dependency Symposium, held December 9, in the Chemical Dependency Section, Department of Medicine, Hennepin County Medical Center, in Minneapolis. The program is as follows:

10:15 AM: Informal Discussion on Chemical Dependency
12:00 PM: "Is Treatment of Alcoholism and Narcotic Addiction Possible?"
2:45 PM: Seminar "New Horizons in Addiction Disorder Research"

Everyone is welcome, and reservations are free to anyone interested in attending. Contact: Milton Bullock, M.D., Hennepin County Medical Center, 612-348-6580 for additional information. (Sponsored by Merrell-National Laboratories).

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THE FARIBAULT CLINIC LTD., has an immediate opening for a Family Physician. The Clinic is in a rural community near the metropolitan area and consists of six Family Physicians, one Surgeon and two Internists. For information please write to: Mrs. Arlene Pfeffer, Faribault Clinic Ltd., 924 N.E. 1st St., Faribault, Minnesota 55021.

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(Continued on page 915)

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DESCRIPTION: Each 15 ml. (one tablespoonful) contains potassium chloride 1.5 Gms., supplying 20 mEq. of elemental potassium, and 20 mEq. of chloride, in a cherry-flavored, palatable base; alcohol 4%. Contains no sugar.

INDICATIONS: Treatment of potassium deficiency occurring especially during thiazide diuretic or corticosteroid therapy, digitalis intoxication, low dietary intake of potassium, or as a result of excessive vomiting and diarrhea. Other causes of hypokalemia are fistulae, laxative abuse, villous adenoma, familial periodic paralysis, hyperthyroid periodic paralysis, insulinoma, primary aldosteronism or secondary aldosteronism, Cushing's Disease, renal potassium wasting conditions such as potassium wasting nephritis, and alkalosis.

CONTRAINDICATIONS: Impaired renal function, untreated Addison's Disease, dehydration, heat cramps and hyperkalemia.

PRECAUTIONS: Potassium chloride should be administered with caution and adjusted to the requirements of the individual patient, since the amount of deficiency and corresponding daily dose is often not known. Excessive or even therapeutic doses may result in potassium intoxication. The patient should be checked frequently and periodic ECG and/or plasma potassium levels made. High plasma concentrations of potassium ion may cause cardiac depression, arrhythmias or arrest. Use with caution in patients with cardiac disease. In hypokalemic states, attention should be directed toward the correction of the frequently associated hypochloremic alkalosis.

ADVERSE REACTIONS: Vomiting, nausea, abdominal discomfort and diarrhea may occur. Symptoms and signs of potassium intoxication include listlessness, mental confusion, paresthesia of the extremities, weakness of the legs, flaccid paralysis, fall in blood pressure, cardiac arrhythmias, and heart block. When hyperkalemia exists, it should be promptly treated with the discontinuance of potassium administration or other steps to lower serum levels if indicated, since sudden shift in plasma levels may induce potentially dangerous cardiac arrhythmias.

DOSAGE AND ADMINISTRATION: One tablespoonful of 15 ml. (equal to 20 milliequivalents) diluted in a 4 ounce glass of water, tomato or orange juice twice daily after meals will be sufficient to replete potassium losses in most hypokalemia patients. Some patients (approximately 30 percent), will require a dose of 15 ml. t.i.d. to reverse diuretic-induced hypokalemia patients. However, these patients require close supervision to avoid the possibility of potassium intoxication. Patients should be cautioned to follow directions implicitly in regard to dilution of Kay Ciel Elixir to prevent gastrointestinal injury.

CAUTION: Federal Law prohibits dispensing without prescription.

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"Potassium chloride is preferred to other salts of potassium since, in most hypokalemic states, hypochloremia is also present and chloride ion is needed to allow complete potassium replacement."[1]

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"In general, the chloride lt is preferable because of ie participation of chloride the renal conservation of otassium."[2]

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ot detacided ertew eb ot su orf rehtar si

Lauqe detaere era nem lla taht noit isoprop
eht ot detacided nda ytrebil ew deviecnoc,
noitan wen a thenitnoc no htruofthgourb srehtaf ruo oga. Sracy neves dna erocsruof, htrar eet morf hsire ton llahs elps eht rof, elpoep eht yb, elpoep et fo tnemnrevog taht dnamodeerf fo htrib wen ewah llahs rednunoitan taht niav.

Ni deid evah ton llahs daed eseht taht evloser ylhgir eb noitaved fo erusaem lluf tasl eht evag yeht heihw orrf esuac taht ot eesaereni ekas ew daed deronoh eseht.

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Thguof oho yeht heihc krow edosinif nu eht ot ereh detacided eb. Ot rehtar gnivil os rof si ti, ereh did ydeht taw tegrof reven nac it tub, erch yas ew tahw rebmember gnol ron, eton elttits dlrow eht tcarted.

Ro dda ot rewop roop ruo vcoba raf, ti detarcesnoc evah ereh delggurth. Dna gnivil nem evarb eht dnuard sint wollah tonnac, ew etarcesnoc tonnac ew esren regral a ni tub od dluohs ew taht reporp dna.

Gnittif rehtegotla is iti evil thgim noitta taht sevil rieht evag ereh ohow esoht fo ecalpgnitser lanif a sa, dleif taht fo noitropet a etacided ot. Kom evah raw taht fo dleifelttab taerg a no tem eca ew, erudne gnol a nac detacided os ena deviesnoc. Brosba os noitan yna ro taht rehtehw gnitset dregn.

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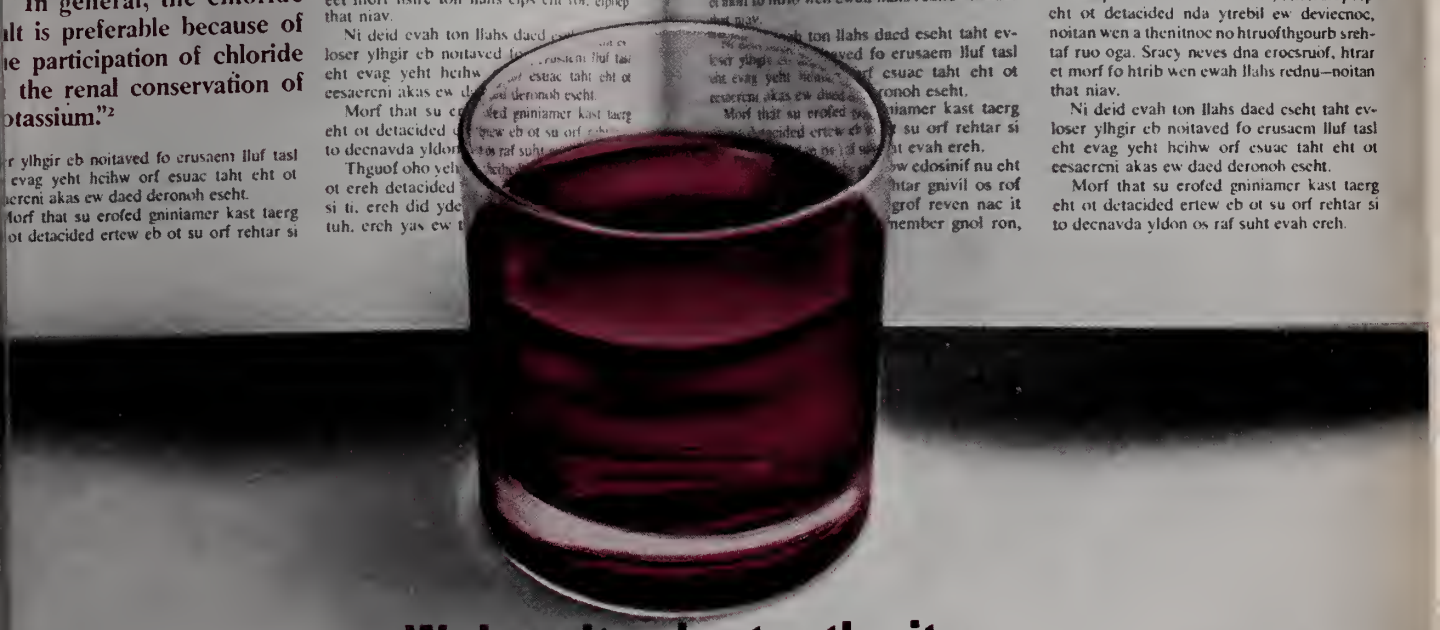
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Special Article

Comprehensive Mental Health Planning in a Children's Hospital

JACK V. WALLINGA, M.D.*

Emotional trauma predictably occurs in children who are psychologically vulnerable because of hospitalization, illness and surgery. There are many ways to prevent or minimize the effects of such experiences. An innovative approach to meeting children's total emotional needs in a pediatric hospital is presented.

THE MINNEAPOLIS CHILDREN'S Health Center and Hospital is a newly constructed pediatric hospital specifically designed, architecturally and philosophically, to help children to master the emotional trauma of hospitalization and surgery. This 107 bed hospital was opened in January of 1973. It incorporates many ideas already in use in other pediatric centers but it is unique in its approach to permeate the entire health center with positive, sensitive mental health attitudes and practices.

Hospitalization Is Upsetting

Children's Health Center is a new kind of hospital experience for children. We have known for over 25 years that hospitalization upsets children[1-3] and that emotional consequences often persist after return home.[4] Among the prominent causes of difficulty are the child's anxiety about separating from parents, lack of familiarity with hospital environment and procedures, distorted expectations about what will be done, anxiety of parents communicated to the child, and lack of sustained relationships with nurses. Pre-school children are especially upset by separation from parents. Latency age children, five to 12 years old, are more concerned with the possibility of disfigurement, mutilation, and loss of body parts.

Adolescents become anxious about losing control-over their environment and specifically over what is done to them. We tried to plan a program that would meet children's needs of all ages.

Primary Prevention

Early in the planning of Children's Health Center the NIMH Publication "Red is the Color of Hurting"[5] was adopted as a guide for incorporating primary prevention in mental health into the entire facility. A planning committee, comprised of representatives from pediatrics and the mental health disciplines, felt a pervasive emotional sensitivity could be best achieved by having a mental health specialist (ecologist) at the hospital administrative level who would primarily be concerned with over-all philosophy, prevention, personnel selection, and educational programs. A separate mental health staff, on a departmental level, responds to specific outpatient and inpatient diagnostic, treatment and consultation requests.

The planning committee was also involved early with architectural design and decor. The hospital is attractively decorated to present a warm, colorful, appealing appearance to children. The walls are painted in bright colors, and carpeting is used extensively in the hallways and bedrooms. Pictures painted by Minneapolis school children are hung in halls and rooms throughout the hospital and add to the feeling of a "children's place."

Environmental Appeal

As children approach the building a large indoor-outdoor play area first catches their interest. When they leave the elevator on a typical ward floor, a large inviting playroom is seen before the bedrooms and nursing station become apparent. On each ward the nursing station is open and centrally located. Every patient room, as well as some parent waiting areas, has color TV. These TV sets may be used later for closed circuit health educational materials as well as entertainment.

*Director of Child Psychiatry, Minneapolis Children's Health Center, and Clinical Associate Professor, University of Minnesota, Minneapolis.

See editorial, page 891.

Traffic patterns in the hospital are designed so that outpatients and visitors use different corridors and elevators than do inpatients being taken to surgery or Xray. It was felt important to protect the very sick or apprehensive preoperative child from the whispers and stares of strangers and also not to expose visitors and children coming for routine outpatient visits to the possible trauma of seeing seriously burned or disfigured children.

Every effort is made to avoid the traditional institutional appearance. Nurses and other personnel wear colorful smocks which are color coded to identify their function, and which they individually decorate. The wearing of white uniforms is discouraged throughout the hospital. Young children are more often transported in red wagons than in wheel chairs or litters. Even the admission and bookkeeping areas, although at the front entrance, are designed to be casual and inconspicuous. Frequently older children have made many visits to the third floor outpatient clinics without realizing that they were in a hospital.

It requires much more than just a pleasant physical setting to minimize the emotional trauma that children experience with hospitalization. We know that all of the rules, regulations, procedures, and practices of a hospital directly affect the patients so these need to be both initially and continually monitored for their emotional implications —one of the important functions of the mental health ecologist. Delay during the admission procedure may increase anxiety so, on routine admissions, the paper work is largely completed in advance. In an emergency situation the child is often taken directly to his bed and the admission forms are completed there or later with the parents.

Since separation is one of the primary causes of anxiety in younger children who are hospitalized, rooming-in for parents is readily available. With young children, the separation aspect of being hospitalized may cause more anxiety than the medical procedures themselves. For parents who don't wish to room-in there are no visiting hour limitations. Visiting is encouraged at any time, and there are no age limits on visiting. We recognize that siblings often have to see the sick child in order to deal with their own fears about what may be happening. They may be involved in the dying process of one of their family. Doctors and nurses have not only become accustomed to the inconvenience of having parents always around, but more important, increasingly see the value of parents having easy access to their sick child.

Early Intervention

We were especially concerned about the vulnerability of children scheduled for elective surgery. Since children may be upset by the unexpected, we try to prepare them and their parents as much as possible for what will take place. Latency age children especially fantasize and anticipate events quite differently from what reality holds in store. Their anxiety about mutilation can be high. If they have an opportunity, however, to express their fears either by talking or playing out their feelings, the "working through" of the difficult experience helps them cope with it more easily. Based on this rationale, on Saturday mornings there is a pre-admission tour to which all children scheduled for future admission are invited. In small groups with their parents and often with their siblings or even grandparents, they tour the admission area, x-ray department, playrooms, the wards, the anesthesia induction area and the waiting room where their parents will be while they are in surgery. Following the tour and some refreshments, the children have a chance to play doctor or nurse on trained mental health volunteers. At this time they enjoy familiarizing themselves with stethoscopes, syringes, surgical caps and masks, and blood pressure cuffs, all things they will encounter during their hospitalization.

During this time the parents meet with a nursing supervior and one of the mental health staff to discuss the meaning of hospitalization to the child, its possible psychological effects, and how parents might better prepare their child to cope with surgery. Some explanation is given about the fears and fantasies that children may have about the forthcoming experience and also about the kinds of regressive behavior problems that may appear upon return home after discharge. The parents also have an opportunity to ask about and relieve many of their anxieties about hospital rules and procedures, and often have questions answered that were not resolved in the doctor's office.

When a child is unusually anxious pre-operatively, an individual appointment with one of the mental health staff may be arranged, without charge, before admission at the request of either the parents or the doctor. In such a visit we try to determine the source of the child's anxiety, and find out what his fantasies are about the forth-

coming hospitalization and surgery. Then we explain and clarify what actually will take place, perhaps with drawings, a play doll family, or other play materials depending on the child's age so that he may be reassured specifically regarding what is going to be done to him.

In extending this preventative preparation program into the community, public health nurses have become involved in visiting children and their families when a serious procedure such as cardiac surgery is first anticipated. They follow the children in regular visits before, during, and after hospitalization and offer both medical and emotional support and instruction.

Staff Sensitivity

Collaboration between psychiatry and anesthesiology has been especially rewarding with sensitive and innovative approaches resulting. The anesthesiologist visits the child and his parents before surgery at which time explanations and reassurances are offered. Mothers frequently accompany young children to the anesthesia induction area where a child may even be anesthetized in his mother's arms. If parents are uncomfortable about being involved, the anesthesiologist may carry the child himself to the induction area. Children are anesthetized before entering the surgical suite. A child who seems to be very heavily invested emotionally in a particular demand may be accommodated. For example, a boy who wanted to keep his pants and cowboy boots on for his ear surgery, awoke post-operatively to find his pants and boots still on. Four to six year old boys will sometimes keep their pajama bottoms on during their tonsillectomy, for instance, to help reassure them about the integrity of their genitals. Children can wear their own pajamas in the hospital, and they are encouraged to bring their favorite toy or comfort object with them no matter how large it is. Often they are clutching their most reassuring possession while they fall off to sleep in anesthesia.

Surgeons are encouraged to talk with the parents immediately after each operation is completed rather than doing several consecutive cases. The importance of keeping communication open between the parents' waiting room and the operating room during surgery is recognized and particularly if there is some inadvertent delay, parents are informed to allay their anxiety.

To further minimize the trauma of the child being separated from his parents, outpatient surgery has been used extensively at Children's Health Center; over 30 percent of surgical procedures use the short stay unit.

During hospitalization when a child has emotional reactions to his experience the nursing staff has been trained to recognize problems and encouraged to help the child express his feelings. Some children write about their stay, others draw pictures of their experience or otherwise act out in play what is going on in their emotional life.

When parents are present or rooming in for lengthy periods, particularly with seriously injured or terminally ill children, pathologic parent-child relationships and parental guilt or rejection may become obvious and these are then available for efforts at intervention. For situations like these which may be beyond the expertise of the nursing staff, each ward has one of the mental health staff assigned to it for liaison, informal consultation, ward staff training, and for preliminary intervention in difficult situations.

Parent discussion and support groups have been used successfully, particularly for those who have infants in the neonatal intensive care unit or those with children who have terminal illnesses. We recognize that serious illness or extensive surgery in a child may precipitate marital disruption and even family disintegration. With a resulting significantly higher divorce rate, early treatment is essential in these instances if it is to be effective.

Children's Health Center has no specific psychiatric inpatient ward. Children with psychiatric problems may be admitted to any of the wards but usually there are accompanying physical or psychosomatic conditions. Emphasis is directed toward the emotional and psychiatric needs of all children in the hospital. Those referred primarily for psychiatric problems receive outpatient diagnostic evaluation and treatment as needed. This is consistent with one of the original goals of Children's Health Center, namely to keep children out of the hospital whenever possible.

The mental health staff provides the traditional clinical functions including psychology, psychiatry, and social work services; in addition, the staff closely collaborates with and provides support for the ecology and prevention programs. Pediatric neurology, other pediatric sub-specialties, audiology and speech therapy are all closely coordinated with the mental health clinic program. Hospital social service is administratively and

functionally a part of the mental health department. The hospital director of social service is also the chief psychiatric worker. The recreational therapist is attached to the mental health department and play is used for its therapeutic as well as its recreational value.

Staff Training

In order for a health center to be sensitive to the emotional aspects of health care delivery it is essential that the staff be knowledgeable and motivated. The mental health program at Children's Health Center includes the education of hospital staff as a primary objective. A mental health grand rounds conference is held regularly on subjects such as child rearing, growth and development, the effects of separation and hospitalization and surgery, and dealing with the dying patient and his family. Typical adjustment and behavioral problems of children are also presented.

Special seminars may be focused on particular child care problems such as the seriously burned child who may especially arouse negative feelings in the nursing staff, feelings which can reverberate detrimentally to the patient if not quickly dealt with. The importance of coordination of patient care is stressed and implemented often by the mental health liaison person on the ward who is in an advantageous position to have an overview of the roles, overt and covert, that various people play.

Human Ecology

Efforts to humanize the hospitalization of children produce many benefits. Children adapt more comfortably to the hospitalization experience. They accept painful and frightening procedures more easily. Psychologically adjusted children recuperate faster, and length of hospital stay is consequently shortened. Parental resistance to allowing necessary care for the child is reduced.

Perhaps more important, the intimate observation in the hospital of parent-child and family interactions provides many insights and even diagnostic clues that may clarify the reasons for vague somatic symptoms in the absence of physical findings and also may reveal reasons for exacerbations in some chronic illnesses. This awareness of the needs of children in the hospital has arisen only in the last three decades. Out of this awareness an increased sensitivity to children's needs as well as to the needs and feelings of their family allow many benefits to accrue beyond just the solution of a child's medical-surgical problem.

Summary

Minneapolis Children's Health Center uses a unique approach to permeate the entire facility with a mental health sensitivity. The design of the building, its decor and furnishings, and its policies and procedures, attitude and philosophy are all planned with awareness for children's emotional as well as medical needs. An acute sensitivity to the feelings of siblings and parents are an integral part of the philosophy. Specific efforts are directed toward helping children anticipate hospitalization and surgery; supporting their emotional adjustment during hospitalization; and helping children and their parents with residual psychological reactions after they return home.

To minimize the need for hospitalization outreach, outpatient, and short stay programs are emphasized. In a comprehensive program of this sort there are additional opportunities to detect and institute preventative measures or early intervention for problems in the child or in the family which otherwise might have gone undetected.

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Howard L. Horns, M.D.

Dr. Howard L. Horns, internist at the Nicollet Clinic in Minneapolis, was appointed by the Federation of State Medical Boards to represent them on the Liaison Committee on Continuing Medical Education of the Coordinating Council on Medical Education.

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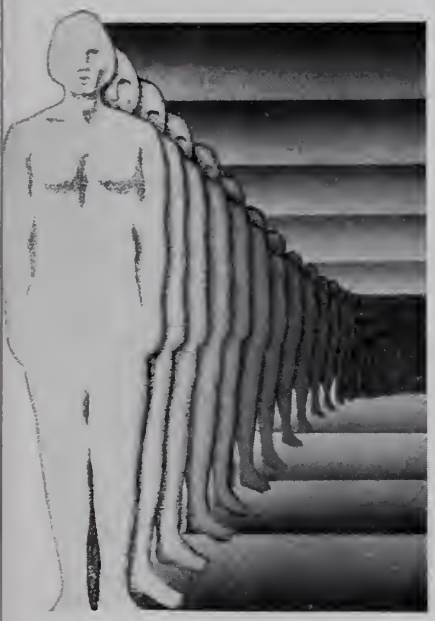
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Indications: Relief of anxiety and tension occurring alone or accompanying various disease states.
Contraindications: Patients with known hypersensitivity to the drug.
Warnings: Caution patients about possible combined effects with alcohol and other CNS depressants. As with all CNS-acting drugs, caution patients against hazardous occupations requiring complete mental alertness (*e.g.*, operating machinery, driving). Though physical and psychological dependence have rarely been reported on recommended doses, use caution in administering to addiction-prone individuals or those who might increase dosage; withdrawal symptoms (including convulsions), following discontinuation of the drug and similar to those seen with barbiturates, have been reported. Use of any drug in pregnancy, lactation or in women of childbearing age requires that its potential benefits be weighed against its possible hazards.

Precautions: In the elderly and debilitated, and in children over six, limit to smallest effective dosage (initially 10 mg or less per day) to preclude ataxia or oversedation, increasing gradually as needed and tolerated. Not recommended in children under six. Though generally not recommended, if combination therapy with other psychotropics seems indicated, carefully consider individual pharmacologic effects, particularly in use of potentiating drugs such as MAO inhibitors and phenothiazines. Observe usual precautions in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

Adverse Reactions: Drowsiness, ataxia and confusion may occur, especially in the elderly and debilitated. These are reversible in most instances by proper dosage adjustment, but are also occasionally observed at the lower dosage ranges. In a few instances syncope has been reported. Also encountered are isolated instances of skin eruptions, edema, minor menstrual irregularities, nausea and constipation, extrapyramidal symptoms, increased and decreased libido—all infrequent and generally controlled with dosage reduction; changes in EEG patterns (low-voltage fast activity) may appear during and after treatment; blood dyscrasias (including agranulocytosis), jaundice and hepatic dysfunction have been reported occasionally, making periodic blood counts and liver function tests advisable during protracted therapy.
Usual Daily Dosage: Individualize for maximum beneficial effects. *Oral—Adults:* Mild and moderate anxiety and tension, 5 to 10 mg *t.i.d.* or *q.i.d.*; severe states, 20 or 25 mg *t.i.d.* or *q.i.d. Geriatric patients:* 5 mg *b.i.d.* to *q.i.d.* (See Precautions.)
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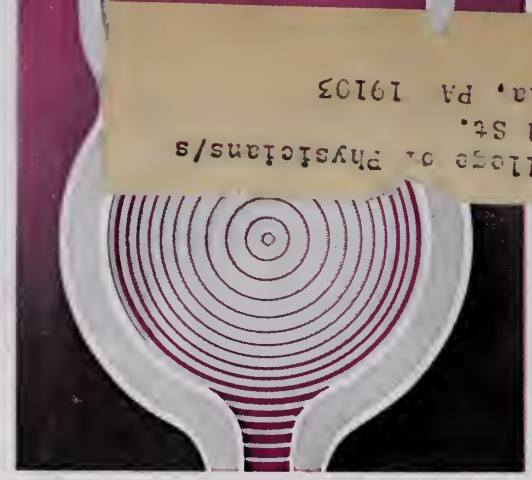
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WHILE YOU ELIMINATE THE PATHOGENS.

FOR THE PAIN

☐ **Early relief of painful symptoms** such as burning and pain associated with urgency and frequency.

FOR THE PATHOGENS

☐ **Effective control of susceptible pathogens** such as *E. coli, Klebsiella-Aerobacter, Staph. aureus, Proteus mirabilis* and, less frequently, *Proteus vulgaris*.

Appropriate antibacterial therapy: Up to 3 days therapy with Azo Gantrisin 4 to 6 tablets *Stat.*, then 2 tablets *q.i.d.*; then 11 days with Gantrisin (sulfisoxazole) may be considered.

AZO GANTRISIN®

(50 mg phenazopyridine HCl and 0.5 Gm sulfisoxazole)

Before prescribing, please consult complete product information, a summary of which follows.

Indications: In adults, urinary tract infections complicated by pain (primarily cystitis, pyelitis and pyelonephritis) due to susceptible organisms (usually *E. coli, Klebsiella-Aerobacter, Staphylococcus aureus, Proteus mirabilis*, and, less frequently, *Proteus vulgaris*) in the absence of obstructive uropathy or foreign bodies. *Important Note:* Carefully coordinate *in vitro* sulfonamide sensitivity tests with bacteriologic and clinical response. Add aminobenzoic acid to culture media for patients already taking sulfonamides. Increasing frequency of resistant organisms currently is a limitation of the usefulness of antibacterial agents including the sulfonamides. Blood levels should be measured in patients receiving sulfonamides for serious infections, since there may be wide variations with identical doses; 12 to 15 mg/100 ml is considered optimal for serious infections; 20 mg/100 ml should be the maximum total sulfonamide level, as adverse reactions occur more frequently above this level.

Contraindications: Children below age 12; sulfonamide hypersensitivity; pregnancy at term and during nursing period. Contraindicated in glomerulonephritis, severe hepatitis, uremia, and pyelonephritis of pregnancy with gastrointestinal disturbances, because of phenazopyridine HCl component.

Warnings: Safe use in pregnancy has not been established. Teratogenicity potential has not been thoroughly investigated. Deaths from hypersensitivity reactions, agranulocytosis, aplastic anemia and other blood dyscrasias have been reported; clinical signs such as sore throat, fever, pallor, purpura or jaundice may be early indications of serious blood disorders. Complete blood counts and urinalysis with careful microscopic examination should be performed frequently during sulfonamide therapy.

Precautions: Use with caution in patients with impaired renal or hepatic function, severe allergy, bronchial asthma and in glucose-6-phosphate dehydrogenase-deficient individuals. In the latter, hemolysis may occur. Maintain adequate fluid intake to prevent crystalluria and stone formation.

Adverse Reactions: *Blood dyscrasias:* Agranulocytosis, aplastic anemia, thrombocytopenia, leukopenia, hemolytic anemia, purpura, hypoprothrombinemia and methemoglobinemia. *Allergic reactions:* Erythema multiforme (Stevens-Johnson syndrome), skin eruptions, epidermal necrolysis, urticaria, serum sickness, pruritus, exfoliative dermatitis, anaphylactoid reactions, periorbital edema, conjunctival and scleral injection, photosensitization, arthralgia and allergic myocarditis. *Gastrointestinal reactions:* Nausea, emesis, abdominal pains, hepatitis, diarrhea, anorexia, pancreatitis and stomatitis. *C.N.S. reactions:* Headache, peripheral neuritis, mental depression, convulsions, ataxia, hallucinations, tinnitus, vertigo and insomnia. *Miscellaneous reactions:* Drug fever, chills, toxic nephrosis with oliguria and anuria, polyarteritis nodosa and L.E. phenomenon. Due to certain chemical similarities with some goitrogens, diuretics (acetazolamide and thiazides) and oral hypoglycemic agents, sulfonamides have caused rare instances of goiter production, diuresis and hypoglycemia. Cross-sensitivity with these agents may exist.

Dosage: Usual adult dosage for acute, painful phase of urinary tract infections is 4 to 6 tablets initially, then 2 tablets four times daily for up to 3 days. If pain persists, causes other than infection should be sought. After relief of pain has been obtained, continued treatment of the infection with Gantrisin (sulfisoxazole) may be considered.

Note: Patients should be told that the orange-red dye (phenazopyridine HCl) will color the urine soon after ingestion.

How Supplied: Tablets, each containing 0.5 Gm sulfisoxazole and 50 mg phenazopyridine HCl —bottles of 100 and 500.

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